Clinical features presented to primary care prior to diagnosis of giant cell arteritis: an electronic health records study

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A thesis submitted in fulfilment of the requirements of the degree of Doctor of Philosophy

December 2021

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Abstract

Background: Giant cell arteritis (GCA) is the most common form of medium and large vessel vasculitis. This condition is associated with serious complications, such as blindness if left untreated, and is therefore considered a medical emergency. However, GCA remains difficult to diagnose, in part, due to the wide variation of presenting symptoms, resulting in some patients facing significant diagnostic delay.

Aim: To evaluate clinical features experienced by patients prior to a diagnosis of GCA.

Methods: Four studies were undertaken. Firstly, a systematic review and meta-analysis of clinical features previously associated with a diagnosis of GCA. Subsequently using the Clinical Practice Research Datalink (CPRD), the remaining three studies investigated; the trends in incidence of GCA; the association of individual clinical features on the subsequent diagnosis of GCA; and finally, combinations of presenting clinical features prior to a GCA diagnosis.

Results: The systematic review found 30 distinct clinical features, with the strongest pooled association for jaw claudication and elevated ESR. A total of 9205 GCA cases were identified from 1990-2017 in CPRD. Consultation incidence of GCA was 1.46 per 10,000 person-years in 2017. In the CPRD analysis, individual features most strongly associated with GCA prior to diagnosis were headache, hypertension, and visual impairment. Application of latent class analysis (LCA) suggested five distinct patterns of presenting features; polymyalgia rheumatica (PMR), hypertension and multiple other features, single or no feature, hypertension, and elevated ESR.

Conclusion: GCA remains a difficult condition to recognise in primary care. Clinical features, such as headache, PMR, elevated ESR, and hypertension were consistently identified as important clinical features experienced prior to GCA diagnosis. This thesis has highlighted the need to research patterns of clinical features rather than individual features that occur prior to a GCA diagnosis.

Contents

List of Tables

List of Figures

“Picking the best solution really depended on your definition of best.”

— V.E Schwab, Vicious

Chapter 1: Introduction

1.1 Chapter overview

This chapter will introduce the subject of the thesis, outlining the main aim, specific objectives, and rationale of the work conducted. An overview of the epidemiology of GCA and use of electronic health records in research will also be presented in this chapter.

1.2 Giant cell arteritis

Giant cell arteritis (GCA), also known as temporal arteritis, is the most common form of medium and large vessel vasculitis (Smeeth, Cook, & Hall, 2006). It occurs when arteries, particularly cranial arteries, become inflamed (Carlo Salvarani, Cantini, Boiardi, & Hunder, 2002). It is associated with serious complications, such as blindness, if left untreated and therefore is considered a medical emergency requiring immediate attention if suspected. However, GCA is a relatively rare condition, with the most recent United Kingdom (UK) incidence estimate in the over 50s from 2015 reported as 1 per 10,000 person-years, with higher rates being found in women aged between 70 and 80 years old (Petri, Nevitt, Sarsour, Napalkov, & Collinson, 2015).

1.2.1 Clinical features of GCA

Clinical features of GCA include the symptoms, signs, comorbidities and laboratory tests which occur in patients prior to their diagnosis. In previous literature the term “classic” symptoms of GCA has been used widely to denote those symptoms which more commonly reflect a presentation of GCA. These “classic” symptoms usually include; headache, scalp tenderness, jaw claudication, and visual complications (Mackie et al., 2011; Marí et al., 2009;

Toren et al., 2016). However, the symptoms which can be accepted as “classical” vary throughout the literature. It has also been raised that medical practitioners, such as GPs, may over-rely on these symptoms to diagnose GCA when they are not universally observed in every patient with GCA (Chean et al., 2019; Ezeonyeji, Borg, & Dasgupta, 2011b). This potential for over reliance on clinical features that may not be present in every GCA patient can potentially lead to increased diagnostic delay for patients.

GCA symptoms which have previously been reported to have a high association with the condition include; new onset headache, jaw claudication (pain in jaw whilst chewing), temporal artery abnormality (a temporal artery that is tender, swollen, or protruding), visual disturbances including diplopia (double vision), and blurred vision (NICE CKS, 2020; Smetana & Shmerling, 2002). However, the prevalence and strengths of association of these symptoms in patients with GCA varies between studies. Additionally, inflammatory markers (classically erythrocyte sedimentation rate (ESR) but also C-reactive protein) are almost universally raised (Smetana & Shmerling, 2002).

The prevalence of clinical features vary greatly by study. For example, amongst confirmed cases of GCA in secondary care, the proportion of patients reporting headache can range from 52.4% (Toren et al., 2016) to 92.9% (Duhaut, Pinede, et al., 1999), and visual disturbances in biopsy proven GCA cases can vary between 30% (Gabriel, O’Fallon, Achkar, Lie, & Hunder, 1995) and 60% (Chmelewski, McKnight, Kevin, Agudelo, & Wise, 1992). Other commonly reported symptoms of GCA include fever, weight loss, and other constitutional symptoms. Furthermore, many of these symptoms are commonly seen in UK primary care and are frequently linked to other, more prevalent conditions than GCA in the UK population. For example, cancer is more prevalent than GCA and is associated with

unexplained weight loss (Moller, Flatt, & Moran, 2011), and headache may represent a malignant primary cancer or more likely metastatic disease in such populations.

Reported prevalence of abnormal temporal artery also varies, with current estimates from secondary care of between 10% (Gabriel et al., 1995) and 75% (Marí et al., 2009), and inflammatory markers, such as elevated ESR, have high variation between previous studies, with estimates ranging from 40% (Chmelewski et al., 1992) to 98% (Rivero Puente et al., 2001).

A comorbidity commonly linked with GCA is polymyalgia rheumatica (PMR). PMR is the most common inflammatory rheumatic disease affecting patients over the age of 50 years, with a UK incidence of 95.9 per 100,000 person years in the over 40s (Partington, Muller, Helliwell, Mallen, & Abdul Sultan, 2018). Common symptoms include shoulder and/or pelvic girdle ache, morning stiffness, and raised inflammatory markers (Helliwell, Hider, Barraclough, Dasgupta, & Mallen, 2012). Although no common biological pathway has been defined to explain the association between GCA and PMR, PMR type symptoms have been frequently shown to occur, with one study indicating between 40% and 60% of GCA patients developing symptoms of PMR during the course of their illness (Hassan, Dasgupta, & Barraclough, 2011). In a study looking into the comorbidities considered to be associated with GCA, PMR was found to be the most prevalent in the GCA population (Petri *et al.*, 2015) and it has been reported that patients who have a history of PMR have been more rapidly diagnosed with GCA (Mackie *et al.*, 2011). Prevalence estimates of PMR prior to a diagnosis of GCA have predominately been conducted in secondary care, usually at the time of GCA diagnosis, and therefore there is no information available on how long a patient has had PMR type symptoms prior to their GCA diagnosis. A study conducted using primary care records could explore the relationship between PMR and a GCA diagnosis further.

Other comorbidities reported in GCA patients before their diagnosis include cardiovascular diseases and diabetes, but wide ranging estimates from these studies have also been reported. Prevalence of cardiovascular diseases (conditions affecting the heart or blood vessels, such as a stroke) amongst GCA patients prior to their diagnosis has been reported to be 4% (Sun, Ma, Zheng, Tian, & Zeng, 2016) and 22% (Unizony et al., 2017), and between 5% and 37% for diabetes (Espitia et al., 2012; Pugnet, Sailler, Bourrel, Montastruc, & LapeyreMestre, 2015), a common condition that causes a patient's blood sugar level to become too high (NHS, 2019).

1.2.2 Diagnosis

Identifying GCA in primary care remains challenging due to the spectrum of clinical features reported to be associated with GCA (Petri et al., 2015; Smetana & Shmerling, 2002). Symptoms generally thought to be indicative of GCA are a headache (often in the temporal area), visual symptoms, and jaw claudication (Smetana & Shmerling, 2002). However, research has found that there are many other symptoms that could be associated.

In 2002, Smetana & Shmerling examined the role of different clinical features in determining a diagnosis of GCA. The clinical features with the highest prevalence in patients prior to GCA in this review were any headache (76%), weight loss (43%), and fever (42%). Although jaw claudication is thought to be indicative of a GCA diagnosis, Smetana & Shmerling found that the prevalence was relatively low, but found that it was highly predictive of a positive temporal artery biopsy. The prevalence of any visual symptoms in this review was equally low, and it was diplopia that was found to have a higher predictive value of a positive temporal artery biopsy than any other visual symptoms (Smetana & Shmerling, 2002). In line with these findings, guidelines used by healthcare practitioners to identify and diagnose

patients with GCA include a range of clinical features that are thought to be associated with a GCA diagnosis.

In the UK, the National Institute for Health and Care Excellence (NICE) provide evidence-based best practice guidelines for diagnosis, management, and treatment for most clinical conditions seen in the UK, for both primary and specialist care settings. For GCA, NICE recommends to use the patient's headache symptoms (of new onset and considered a red flag symptom in need of urgent attention in someone over 50), temporal artery abnormality, and age (GCA is rare in people under the age of 50 (Petri et al., 2015)), which are identified in primary care, as guidance for diagnosis/referral (Mackie et al., 2020; NICE, 2014; NICE CKS, 2020). In order to aid in the prompt diagnosis of the patient, blood tests such as C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR) are also recommended (NICE CKS, 2020).

One of the tools used to identify GCA is the American College of Rheumatology (ACR) classification criteria. This was developed to create a standardised phenotype for research into different forms of vasculitis, and has been the usual standard for many studies previously. However, it has also been used (potentially inappropriately) for diagnostic purposes (Gene G. Hunder et al., 1990). The criteria include age of the patient (over 50 years), presence of headache, and laboratory measurements such as elevated ESR, and temporal artery abnormality (Gene G. Hunder et al., 1990).

Referral to secondary care is only the first part of the diagnostic pathway of GCA. In secondary care the current gold standard diagnostic method to determine the presence of GCA is a temporal artery biopsy, though increasingly ultrasound is seen as a viable method. On some occasions diagnosis may also be confirmed by a rheumatologist or other specialist (NICE CKS, 2020). Further details will be discussed in Chapter 2.

1.2.3 Diagnostic delay

As a result of the difficulties described in achieving prompt diagnosis of GCA, diagnostic delay (the time from symptom onset to final diagnosis) continues to be a major concern in the diagnosis and treatment of GCA.

A systematic review and meta-analysis conducted by Prior et al (2017) investigated the extent of diagnostic delay in GCA. The review identified 22 articles that sufficiently reported information about diagnostic delay in patients diagnosed with GCA. Overall, the study found a mean of 9.2 weeks of diagnostic delay from symptom onset in all GCA patients. However, there was variation in diagnostic delay depending upon the clinical feature a patient presented with. Patients with cranial symptoms, such as headache and scalp tenderness, had a shorter time from onset to diagnosis (7.7 weeks), compared to those without cranial symptoms, where the diagnostic delay was more than double (17.6 weeks). This review also found that patients presenting with a headache had a much shorter time between onset and diagnosis than those who did not present with a headache.

It remains unclear where on the clinical pathway diagnostic delay for patients with GCA occurs. Whether it is that patients self-manage the initial symptoms and only visit a GP when they do not improve, or exacerbate, or whether it is the time from referral from primary care to secondary care, can only be hypothesised (Raza et al., 2011).

As will be described in further detail in Chapter 2, diagnostic delay in GCA remains a concern given that it is a medical emergency and that the many presenting clinical features, sparse levels of evidence of their prevalence and strength of association can cause difficulties in achieving a prompt diagnosis in primary care or referral for further investigation. In order to investigate which clinical features are associated with a GCA diagnosis, information about a

patients' diagnostic pathway from initial symptom onset to final diagnosis should be examined. This is something which can be achieved through the use of primary care medical records.

1.3 Electronic health records

Primary care electronic health records (EHR) are a useful longitudinal resource to examine conditions which are rare in the population, such as GCA, where recruitment of enough cases may be difficult using a prospective study design. Information on patients prior to their diagnosis of GCA is available in EHR, due to patients typically remaining registered at their practice for long periods of time, and is free from the problems experienced by some research study designs, where certain participants may not provide the requested data (non-response bias) or struggle to accurately recall information from their past health (recall bias). In the UK, 95% of the population is registered with a general practice (NHS, 2012). EHR contain records of diagnosis, disease management, referral information, and prescription details from patient consultations (Cowie et al., 2017), from a relatively stable population that are followed over a long period of time (R. S. Evans, 2016; Herrett et al., 2015). There are several EHR databases that contain primary care consultation data available for the purposes of research in the UK, with some of the most widely used being; the Health Improvement Network (THIN), the Clinical Practice Research Datalink (CPRD), QResearch, and ResearchOne. EHR databases can, and have been used to investigate consultation history prior to the onset of a disease, as well as its progression (Durand & Thomas, 2012; Muller et al., 2019). Since the main concern of GCA lies in the process of events from symptom onset to the initiation of treatment, via the point of diagnosis, medical records

from primary care can potentially be used to identify clinical features that may contribute to a more prompt diagnosis of GCA (Barnes et al., 2020; Mallitt et al., 2018; Rees et al., 2017).

1.4 Aims and objectives of the thesis

The aim of this thesis is to examine and quantify the association between relevant clinical features experienced by patients prior to a subsequent diagnosis of GCA. This will be achieved through four main objectives:

1. To systematically review current evidence on the prevalence and association of clinical features reported in patients with GCA prior to diagnosis.
2. To quantify the UK incidence and prevalence estimates of GCA using longitudinal primary care consultation data.
3. To measure the frequency and association of individual clinical features prior to a GCA diagnosis using longitudinal primary care consultation data.
4. To investigate common patterns of presenting clinical features prior to a GCA diagnosis using longitudinal primary care consultation data.

Two secondary methodological objectives will also be undertaken:

1. To assess the potential of using routine primary care EHR data to investigate clinical features prior to a GCA diagnosis, and other similar difficult to diagnose conditions.
2. To assess the use of Latent Class Analysis (LCA) applied to primary care EHR as a method to derive patterns of clinical features in GCA (and other similar conditions).

1.5 Thesis rationale

One of the main barriers facing current GCA research is diagnostic delay. Due to the risk of permanent visual impairment or complete sight loss, GCA is classed as a medical emergency, and therefore treatment should be prompt (Mackie et al., 2020).

In order to consolidate the evidence around the varying clinical features reported prior to a diagnosis, an extensive review of the literature is required. The clinical features found by this review will inform the subsequent studies conducted in this thesis, by highlighting which clinical features have previously been examined, and guiding the selection of features for further investigation.

The UK has an ageing population and hence more people may be at risk of a GCA diagnosis than there was at the time of the previous study (Petri et al., 2015), which included data up to 2011. GCA is more likely in patients aged between 70 and 80 years. Given the lack of current incidence estimates in the UK population, and to assess whether the trends found in the previous study by Petri et al (2015) have remained the same over time, the analysis will start by deriving the current incidence/prevalence estimates.

Due to the problem of diagnostic delay for patients with GCA, this thesis will endeavour to provide new information to support GPs in identifying patients with potential GCA by assessing associations of individual clinical features, and patterns of presenting features in the time-period prior to a GCA diagnosis. Previous studies that have investigated the association/prevalence of clinical features and a GCA diagnosis are largely based on small sample sizes from secondary care (Mohamed & Bates, 2002; Zenone & Puget, 2013), hence a study including a much larger sample size, available from EHR, is needed, with the ability to accurately assess the time between symptom onset and GCA diagnosis. Investigating the effect of clinical features that have not been previously thoroughly investigated, or few

previous studies have included, on a diagnosis with GCA in tandem with other more accepted clinical features could allow for a more robust and prompter diagnosis of GCA. Finally, in order to be able to examine patterns of clinical features, the role of individual clinical features on a GCA diagnosis must first be examined.

1.6 Thesis overview

This thesis will investigate the clinical features presented to primary care prior to diagnosis of GCA. The first two chapters of this thesis will provide a detailed background into GCA and how its epidemiology can be investigated via primary care records, current methods of diagnosis, and treatment pathways available to patients. A systematic review of previously published literature will then be conducted in Chapter 3 to identify previously reported presenting clinical features of GCA. Chapter 4 will introduce the concept of the electronic health record database to be used throughout the thesis. Three studies will then be undertaken using primary care data from electronic health records to investigate GCA in the UK. Chapter 5 will include the methods, results, and discussion of a consultation incidence and prevalence study using electronic health records. In Chapter 6, a case-control study will be conducted to investigate the association between individual presenting clinical features and a subsequent diagnosis of GCA. The final study will be presented in Chapter 7 and will involve applying clustering methodology to identify common patterns of presenting clinical features. Finally, an overview of all findings, and implications for clinical practice and future research will be detailed in Chapter 8.

Chapter 2: Background

2.1 Chapter overview

This chapter will focus on describing the epidemiology and diagnosis of giant cell arteritis (GCA), common clinical features experienced alongside this condition, and the primary management and treatment provided to patients with GCA in the UK.

2.2 Giant Cell Arteritis

Giant cell arteritis (GCA) is the most common medium and large vessel vasculitis, mostly affecting the aorta, branches of the ophthalmic artery, and extracranial branches of the carotid arteries (Baig, Pascoe, Kini, & Lee, 2019; Dasgupta et al., 2010; Lyons, Quick, Sinclair, Nagaraju, & Mollan, 2020). GCA occurs when there is inflammation in the vascular wall, prompting a physiological reaction in the artery that can lead to structural changes, intimal hyperplasia, and luminal occlusion (Weyand & Goronzy, 2000). Such changes in the vasculature can lead to visual loss due to vascular occlusion of ocular arteries, intermittent claudication or angina, and in some cases heart attack and stroke (Weyand & Goronzy, 2000).

2.2.1 Incidence and prevalence of GCA

Overall incidence rates in the UK have been most recently estimated as between 1 and 2 per 10,000 person-years in patients over the age of 40 years (Petri et al., 2015; Smeeth et al., 2006). Both of these studies were conducted using an EHR database, the Clinical Practice Research Datalink (CPRD), and covered the years 1990 to 2001 (Smeeth et al., 2006), and 2000 to 2011 (Petri et al., 2015). GCA onset is typically after the age of 50, but most

commonly affects patients aged between 70 and 79 years, and is more common in females than males (Mackie et al., 2020; Petri et al., 2015; Smeeth et al., 2006).

A study predicting the world disease burden of GCA by 2050 estimated that the incidence of GCA would increase in both Oceania and Europe by 2050, but acknowledged that there were few studies conducted in Asia regarding GCA in the population (De Smit, Palmer, & Hewitt, 2015). Despite this global perspective, incidence and prevalence estimates of GCA varies widely between countries, with this typically being greater in countries where the population is of mainly northern European descent. In Norway the overall average annual incidence of GCA was found to be 1.7 per 10,000 person-years in the period from 1972-2012 for patients aged over 50 years (Brekke et al., 2017). In Sweden the most recent estimates from 1976-1995 show an incidence of 2.2 per 10,000 person-years (Nordborg, Nordborg, & Petursdottir, 2000). A study conducted in Olmsted County, Minnesota, USA, a population of mainly northern European descent, found an age and sex adjusted incidence rate of 1.9 per 10,000 person-years in patients aged 50 years and over (Carlo Salvarani, Crowson, O'Fallon, Hunder, & Gabriel, 2004). Incidence estimates in northern European countries differ from countries in southern Europe, like Italy and Spain. The incidence in Italy has been reported as 0.7 per 10,000 person-years from 1980-1988 (Salvarani et al., 1991), and incidence in Spain is reported as 1.3 per 10,000 person-years from 2001-2005 (Gonzalez-Gay et al., 2007). In Oceania and Asia incidence estimates are lower than Europe and the USA (De Smit et al., 2015). In Australia the incidence estimate is 0.3 per 10,000 person-years in patients 50 years and over (Dunstan et al., 2014). A study comparing the incidence of GCA between Caucasians and Asians found that GCA was 20 times less likely in the Asian population (Pereira et al., 2011). However, this study had a small sample size, and the incidence rate was only available from Japan.

2.2.2 Clinical features of GCA

For the purposes of this thesis, clinical features of GCA will be defined as symptoms (subjective manifestations of an illness such as headache), signs (objective physical manifestations of an illness such as abnormal temporal artery), comorbidities (conditions happening concurrently with a primary condition), and laboratory test findings. The current NICE guidelines indicate that if a patient is over 50 years of age, and presents with either a new onset headache in the temporal area, or temporal artery abnormality, such as redness or inflammation, then GCA should be suspected (NICE CKS, 2020). Other symptoms that may be suggestive of GCA include; constitutional features such as fever, weight loss, and fatigue; features of polymyalgia rheumatica (PMR); abnormal temporal artery; intermittent jaw claudication; and visual disturbances (NICE CKS, 2020).

2.2.2.1 Headache

Headache is widely considered to be the symptom most indicative of the presence of GCA (Mackie et al., 2020). However, previously published studies have found that the prevalence of headache in patients with GCA can range from 52% to 93% (Duhaut, Pinede, et al., 1999; Toren et al., 2016), whilst a further study reported at least 24% of patients diagnosed with GCA can report no headache at all prior to their GCA diagnosis (Smetana & Shmerling, 2002). Low presentation of headache may present issues related to prompt diagnosis, as a previous study investigating the diagnosis and management of GCA in UK primary care showed that GPs potentially over-rely on headache to diagnose GCA (Helliwell et al., 2018).

2.2.2.2 Visual disturbance

In the same study by Helliwell et al (2018), the second most common symptom used by GPs to identify possible GCA was visual disturbances, which are also included in the NICE guidelines as clinical indicators of GCA. GCA is classed as a medical emergency due to the possibility of irreversible visual impairment in patients with GCA (Mackie et al., 2020; NICE CKS, 2020). Patients with GCA can present with a range of visual disturbances from diplopia, through to complete blindness in one or both eyes (NICE CKS, 2020). NICE estimates that blindness in one or both eyes occurs in 20% of GCA patients prior to their diagnosis (Barraclough, Mallen, Helliwell, Hider, & Dasgupta, 2012; NICE CKS, 2020; Salvarani et al., 2005). Previous studies estimate that visual complications occur in between 16 and 30% of patients (Salvarani et al., 2005; Vodopivec & Rizzo, 2018). In a study of patients with GCA, those who had visual complications were less likely to have headaches than those with no visual complications, and the overall incidence of visual complications in the GCA population was found to be 20.9 patients per 10,000 person years (Saleh, Turesson, Englund, Merkel, & Mohammad, 2016). Serious visual complications, such as blindness, are irreversible (Dasgupta, 2010). The key to managing GCA promptly, therefore, is avoiding diagnostic delay and initiating treatment prior to visual disturbances developing.

2.2.2.3 Temporal artery abnormality

Temporal artery abnormality is an indicator of GCA on NICE's list, and the third most commonly used feature to diagnose GCA by GPs (Helliwell et al., 2018). Abnormal temporal artery is a temporal artery that is tender, swollen, or has nodular lesions (Banz & Stone, 2018). Similar to headache, there are a range of prevalence estimates for the presence of an abnormal temporal artery in patients prior to their GCA diagnosis. Previous studies have

reported prevalence estimates of abnormal temporal artery from 19% to 85% of patients prior to a GCA diagnosis (Hayreh, Podhajsky, Raman, & Zimmerman, 1997; Narvaez et al., 2003).

2.2.2.4 Jaw claudication

Another symptom of GCA hypothesised to be related to a subsequent diagnosis is jaw claudication. In the study conducted by Helliwell et al (2018) jaw symptoms were the fourth most common symptom used by GPs to diagnose GCA and Ezeonyeji et al (2011) found that jaw claudication occurred in 48% of patients with GCA (Ezeonyeji et al., 2011b), although this estimate varies between studies (Desmet, Knockaert, & Bobbaers, 1990; A.G Singh et al., 2015). However, jaw claudication has also been shown to have limited usefulness in the aid of a diagnosis for GPs when it is the only feature without any other symptom more commonly associated with GCA and can cause a GCA diagnosis to be missed. (Hassan et al., 2011). For example, Younge et al (2004) found that the combination of jaw claudication and double vision predicted a positive temporal artery biopsy result with 100% specificity and 2% sensitivity (Younge, Cook, Bartley, Hodge, & Hunder, 2004). This implies that jaw claudication may not be as useful as other clinical features to diagnose GCA, particularly as Aiello et al (1993) found that patients presenting with jaw claudication are also at a higher risk of future blindness (Aiello, Trautmann, McPhee, Kunselman, & Hunder, 1993), which may be related to missed or delayed diagnosis.

2.2.2.5 Constitutional symptoms

Other symptoms that are reported in studies and recommended by NICE as potential indicators of GCA include; fever, malaise, anorexia or weight loss, sometimes grouped as

"constitutional symptoms" (Carlo Salvarani, Cantini, & Hunder, 2008). One study found that in a population of GCA patients only 32% presented with constitutional symptoms (Ezeonyeji et al., 2011b). However, Helliwell et al (2018) found few GPs used constitutional symptoms as an indicator for GCA, preferring headache and scalp tenderness (Helliwell et al., 2018). It should be noted that there is no generally accepted definition of which symptoms are included under the term "constitutional symptoms".

2.2.2.6 Comorbidities

A common comorbidity hypothesised to be associated with GCA is PMR. PMR classically presents with stiffness or pain in the neck, shoulders or hips (which is typically bilateral) raised inflammatory markers, and responds dramatically to glucocorticoid treatment (Mackie et al., 2020). It is currently estimated that between 40% and 60% of patients have PMR type symptoms at the time of their GCA diagnosis, and between 16% and 21% of patients with PMR will go onto develop GCA (Christian Dejaco, Duftner, Dasgupta, Matteson, & Schirmer, 2011).

There are few studies which focus on investigating the occurrence and association of other comorbidities prior to a diagnosis of GCA. Petri et al (2015) listed the 25 most frequent comorbidities recorded in a patient's record prior to their diagnosis of GCA. The most common was PMR, followed by chest infection, hypertension, and joint pain. Hypertension, diabetes, and osteoarthritis were also included in the list of 25 most frequently recorded. There have been studies which focus on the occurrence and association of one comorbidity prior to a GCA diagnosis, such as Venous Thromboembolism (VTE), or other vascular conditions (Li, Neogi, & Jick, 2017; Unizony et al., 2017). However, studies that investigate comorbidities prior to a GCA diagnosis are few. It is important to determine which

comorbidities are present prior to a GCA diagnosis, as some GCA treatments can exacerbate pre-existing comorbidities, such as hypertension, and diabetes (Lyons et al., 2020).

2.2.2.7 Laboratory tests

If GCA is suspected based on presenting clinical features, NICE recommends that patients should have an immediate blood test to check for inflammatory markers (NICE CKS, 2020). GCA causes an increase in platelet count, hence higher levels of Erythrocyte sedimentation rate (ESR) are thought to be an indicator of GCA (Mackie et al., 2020). The accepted level of ESR that indicates GCA as a possible diagnosis is ≥50 mm/h (Mackie et al., 2020; NICE CKS, 2020). C-reactive protein (CRP) and plasma viscosity (PV) are also shown to be indicators of a GCA diagnosis (Lyons et al., 2020). A combination of CRP and ESR are thought to have the best sensitivity and specificity for a diagnosis of GCA (Lyons et al., 2020). One study has shown that levels of CRP and ESR were significantly lower in patients presenting with permanent visual loss (Salvarani et al., 2005). Patients with GCA may also show elevated liver function test results, and normochromic normocytic anaemia in their blood test (NICE CKS, 2020).

2.3 Diagnosis of GCA

Diagnosis of GCA can prove difficult due to the inconsistency and wide variation of presenting symptoms. For example, as indicated in section 2.2.2.1 above, not every patient who is diagnosed with GCA will have presented with a headache (Gideon Nesher, 2014), a symptom many would consider a definitive indicator of GCA.

2.3.1 NICE guidelines

NICE guidelines, the main authority for guidance when diagnosing and managing conditions in UK primary care, instructs GPs to immediately refer patients with suspected GCA to a specialist (usually a rheumatologist) on a fast-track pathway if available (Mackie et al., 2020; NICE CKS, 2020). The guidance advises that patients with visual symptoms should be immediately referred to an ophthalmologist. Additionally Patients with suspected GCA should be treated with glucocorticoids without waiting for confirmation of diagnosis from the referral (NICE CKS, 2020). Higher doses of glucocorticoids or intravenous glucocorticoids should be considered for patients with visual symptoms to prevent further sight loss, and preservation of remaining sight. It is generally accepted that a temporal artery biopsy should be conducted on patients with suspected GCA to confirm diagnosis (Hassan et al., 2011). However, NICE do not state a gold standard method of confirming GCA diagnosis and recommend that any patient suspected of having GCA should be immediately referred to a specialist (NICE CKS, 2020).

2.3.2 Classification criteria

A common form of criteria used to distinguish GCA from other vasculitides are the American College of Rheumatology (ACR) classification criteria. This classification is based on the age of the patient, if they are newly presenting with a headache, if they have an elevated ESR, if they have temporal artery abnormality, and an abnormal biopsy result (Gene G. Hunder et al., 1990). Whilst temporal artery biopsies reportedly have a very high specificity (proportion of true negatives correctly identified), of 100% (Davies & May, 2011), it has poor sensitivity (proportion of true positives), which has been reported as low as 39% (Chase, Patel, & Ramsey, 2020).

In the original study to develop the criterion, the authors looked at over two hundred patients with GCA in order to create a classification criteria for GCA compared to control patients with other forms of vasculitides (Gene G. Hunder et al., 1990). Patient information was collected, via questionnaire, from 48 hospital departments in the USA, Canada, and Mexico, to confirm GCA diagnosis through biopsy results, laboratory results, findings from physical examinations, and collate patient demographics (Bloch et al., 1990).

Using two methods, "traditional format" (a rule that usually takes the format "if, for a given subject, at least X out of Y characteristics are present, then classify subject as having Z") and classification trees (built through a process of binary recursive partitioning, which splits data into binary partitions, and iteratively repeats this step until a decision tree has been made) (Bloch et al., 1990), they produced a classification tool made up of 5 criteria. If a patient fulfilled 3 out of the 5 then they were classed as having GCA. The resulting criteria from both methods had sensitivity and specificity above 90%, with slightly better results from the classification tree (Gene G. Hunder et al., 1990).

However, this study had a number of limitations. Only 214 patients with confirmed GCA were used to build and validate the tool, which is a small sample size on which to create classification criteria and could lead to any analysis being underpowered. The criteria have not been extensively validated within a vasculitides population, which it was originally intended for, or within a general population cohort, where it has been subsequently used since its development (Murchison et al., 2012). The criteria have also been used as a diagnostic tool which they were not developed for (Murchison et al., 2012). The tool was only built using samples taken from North America, thereby making its generalisability to European (including UK) populations unclear. It has also been more than 20 years since the tool was developed, making it potentially outdated.

Despite its limitations, it has become the most frequently used classification tool for referral for patients presenting with possible GCA, and has been used to inform the current UK guidelines on GCA diagnosis and management (Dunstan et al., 2014; NICE CKS, 2020; Abha G. Singh et al., 2015; Sun et al., 2016). However, with only 5 criteria on the tool, it may miss other common symptoms reported in GCA patients, such as weight loss, and fever (Mackie et al., 2020).

2.3.3 Temporal artery biopsy

Temporal artery biopsy is the currently accepted gold standard diagnostic test for GCA diagnosis (Chase et al., 2020; NICE, 2014). A temporal artery biopsy involves taking a sample of a patient's temporal artery (Chase et al., 2020). The recommended sample length of a temporal artery biopsy is at least 1cm (Mackie et al., 2020). A positive biopsy sample will show signs of infiltration of the vessel wall by mononuclear inflammatory cells and giant cells (Lie, 1990; Mackie et al., 2020).

Whilst temporal artery biopsies generally have high specificity it can have poor sensitivity, which has been reported to be as low as 39% (Ball, Walsh, Tang, Gohil, & Clarke, 2010; Davies & May, 2011; Karassa, Matsagas, Schmidt, & Ioannidis, 2005; Luqmani et al., 2016). Limitations of a temporal artery biopsy are that it is an invasive procedure (Davies & May, 2011), and complications following the biopsy can arise (Chase et al., 2020). These are mostly common surgical complications such as bleeding, and infection of the biopsy site, but in rare instances can be more serious, such as permanent nerve damage to the facial nerve (Chase et al., 2020).

2.3.4 Ultrasound

Due to the limitations and complications of temporal artery biopsy, ultrasound has recently been investigated as an alternative diagnostic method, with several studies advocating the use of an ultrasound (US) scan to diagnose GCA rather than a temporal artery biopsy.

An initial meta-analysis found the pooled sensitivity of US to be 69% compared to biopsy, which was 55%, and specificity of US to be 82% compared to 94% for a biopsy (Karassa et al., 2005). Another meta-analysis, which only included clinical trials, comparing temporal artery biopsy to US found the sensitivity of US versus a biopsy was 75% and the specificity was 83% (Ball et al., 2010). One pilot study, which included 10 patients with suspected GCA, conducted an US first followed by a biopsy, then measured the sensitivity and specificity of each method (Suelves et al., 2010). The results of this study found no false positives, and both sensitivity and specificity were 100% for the US.

Following on from these initial studies the National Institute for Health Research (NIHR) funded a study evaluating the diagnostic performance and cost effectiveness of US in diagnosing patients with suspected GCA (Luqmani et al., 2016). A total of 35 secondary care centres across the UK were recruited for the study, and a total of 381 patients with suspected GCA were included in the primary analysis. The median age of the population was 71 years, whilst 72% were female. In 70% of patients the results from the US and biopsy were consistent. The sensitivity of a biopsy was 39%, compared to 54% for US. However, the specificity of temporal artery biopsy was 100%, compared with 81% for US. The study concluded that US was more sensitive and cost-effective than temporal artery biopsy, but did highlight that a third of included patients had negative temporal artery biopsy and US results, but were still diagnosed with GCA based on clinical criteria such as ACR. The conclusions of this study support previously published literature that US is more sensitive

than temporal artery biopsy, correctly identifying patients with GCA more frequently than a biopsy; however, the specificity has consistently shown to be lower than that of a temporal artery biopsy (Schmidt, 2018).

In general US has been found to have higher sensitivity, be more cost-effective, and less evasive than a temporal artery biopsy (Mackie et al., 2020) but the sensitivity of US decreases more rapidly after the initiation of glucocorticoid treatment than a temporal artery biopsy (Luqmani et al., 2016). However, the use of a biopsy or US is dependent on an initial suspicion of GCA by a healthcare professional at the primary care level.

2.3.5 Diagnostic delay

As discussed in Chapter 1 section 1.2.3, diagnostic delay has significant implications for patients with GCA as outcomes can be poorer and more serious including permanent visual loss (Ezeonyeji et al., 2011b). Due to the rarity of GCA, and the spectrum of reported early symptoms, patients sometimes face delays in diagnosis. Such delays in other rheumatological conditions, such as rheumatoid arthritis (RA), have been shown to increase the risk of complications (Raza et al., 2011).

A meta-analysis aimed to pool the estimates of diagnostic delay reported in studies which included patients with GCA (Prior et al., 2017). They found that articles stratified GCA patients by cranial symptoms, defined by the presence of scalp tenderness or headache, and non-cranial as presenting with constitutional symptoms such as fever or anorexia. Patients with cranial symptoms had a diagnostic delay of 7.7 weeks from symptom onset, whilst those with non-cranial symptoms waited 17.6 weeks for a diagnosis.

A delay in diagnosis is of concern considering the complications of untreated GCA. Once patients present to their GP with visual problems, or sight loss as a result of GCA, then it may

be too late as these symptoms are often irreversible. Patients with suspected GCA are also susceptible to stroke and aortic aneurysms (J. M. Evans, O'Fallon, & Hunder, 1995)

Diagnostic delay can arise from multiple sources. Raza et al (2011) classified delay into four main areas of delay for referral to a rheumatologists for rheumatoid arthritis (Raza et al., 2011), which translates appropriately to diagnostic delay of GCA and many other illnesses. Sources of delay included; time between onset of symptoms and request by a patient for assessment by a health care professional (HCP), time between request to see an HCP and attending a consultation, time between the initial HCP assessment and referral to a rheumatologist, and the time between referral and being assessed by a rheumatologist. Although there are significant variations in referral pathways for GCA across the UK (Helliwell et al., 2018)(Helliwell et al., 2018)(Helliwell et al., 2018)(Helliwell et al., 2018)(Helliwell et al., 2018) given that GCA is considered a medical emergency the time between deciding to refer and seeing a specialist for diagnostic confirmation needs to be minimised, but treatment should be started immediately. An improved understanding of the clinical features associated with a diagnosis of GCA could therefore have a positive impact on reducing the delay in referral after presenting to a GP.

Not all patients with GCA will present with the same symptoms. Reasons for delays from the onset of symptoms to seeking medical advice and actually seeing a GP are multifactorial. Symptoms such as headache and minor visual impairment, such as blurred vision are possibly ones that a patient would not immediately go to see their GP about. Instead they may self-manage the condition or make an appointment at the optician, assuming it is a minor ailment.

2.4 Treatments

2.4.1 Glucocorticoids

Once a diagnosis of GCA is considered, treatment typically takes the form of Glucocorticoids. These are a pharmaceutical form of steroid hormone (steroids that act like hormones) and are used for a myriad of illnesses and are highly effective at reducing inflammation in immune responses (BNF, 2020). Glucocorticoids have been used to treat a number of diseases, such as asthma, since the 1940s. Possible adverse events encountered from short-term use include myopathy, pancreatitis, and hypertension (Buchman, 2001). Side effects from long-term use can include osteoporosis, gastrointestinal disease, and ophthalmologic events such as glaucoma (Rice, White, Scarpati, Wan, & Nelson, 2017). Although there are several types of glucocorticoid, prednisolone is most commonly used to treat GCA in the UK (Petri et al., 2015). NICE currently recommends patients presenting without visual symptoms should be given 40-60mg of oral prednisolone daily, and patients with visual symptoms should be given a one-off dose of 60-100mg and should be seen by an ophthalmologist on the same day (NICE CKS, 2020). Oral prednisolone is then tapered, ideally within 2 years of first GCA diagnosis (NICE, 2014).

In recent years there has been growing concern around the long-term effects of glucocorticoid use in GCA patients, with a call to investigate how harmful it is (Dejaco *et al.*, 2017). NICE recommends to prescribe this drug to patients with suspected GCA before it has been confirmed by biopsy or further tests (NICE CKS, 2020). In one general population based study that included 4671 GCA diagnosed patients, 99.67% had been prescribed prednisolone (Petri et al., 2015). Glucocorticoids are thought to improve the visual symptoms commonly seen in patients with GCA, and when started on treatment the risk of vision loss becomes low (Salvarani et al., 2005). However, one study has found that it is not the dose, but the

time between the onset of symptoms to first treatment that is more indicative of improvement to visual complications (González-Gay & Pina, 2015). It should be noted that if total visual loss occurs in a patient then glucocorticoids will not reverse this and the aim of high dose glucocorticoids is to limit visual loss progression and preserve any remaining sight (Carlo Salvarani et al., 2008).

Simultaneously with glucocorticoids patients are prescribed a proton pump inhibitor (PPI), for example omeparzole (NICE, 2014). This is because studies have found that high-dose steroids are associated with gastrointestinal ulcerations, and so to protect the stomach PPIs are prescribed (Hassan, Dasgupta and Barraclough, 2011). There have been a number of studies investigating the side-effects of glucocorticoid use (Buchman, 2001; McDonald et al., 2018; Rice et al., 2017), with possible adverse effects of long-term glucocorticoid use including peptic ulcers, myocardial infarction, diabetes, higher risk of infections, and hypertension (Rice et al., 2017). For these reasons it is important to accurately and promptly diagnose GCA, so patients are not being prescribed glucocorticoids when they do not need them.

2.4.2 Tocilizumab

Tocilizumab (TCZ) has been advocated by a number of trials and several studies as an effective treatment for GCA (J. Evans, Steel, Borg, & Dasgupta, 2016; Stone et al., 2017; Villiger et al., 2016; Vitiello et al., 2018). TCZ is a mono-clonal IL-6 receptor blocker that has shown promise in recent studies and trials in the treatment of GCA, and as an alternative to glucocorticoids (Ponte, Rodrigues, O'Neill, & Luqmani, 2015).

Following on from case reports and case series, looking at a small number of patients' response to TCZ (J. Evans et al., 2016; Loricera et al., 2015; S. Unizony et al., 2012), a large

multicentre blinded randomised trial was conducted to investigate the effect of TCZ on disease remission in GCA patients over 1 year (Stone et al., 2017; S. H. Unizony et al., 2013). Patients were allocated on a ratio of 2:1:1:1 to four groups; those receiving weekly tocilizumab plus a 26-week taper of prednisone (group 1), a group receiving tocilizumab every other week plus the 26-week prednisone taper (group 2), a third receiving a weekly placebo plus the 26-week prednisone taper (group 3), and a placebo group receiving a 52-week prednisone taper (group 4) (Stone et al., 2017). The authors of the trial concluded that a regimen of TCZ, whether weekly or every other week, along with a prednisone taper, was superior to prednisone on its own (Stone et al., 2017). The proposed 2 year open-label follow-up of this trial, which aimed to look at long-term safety and efficiency of tocilizumab is completed as of 2020. In the UK, as of March 2020, NICE do not currently have TCZ on their guidelines for the treatment of GCA.

2.5 Evidence gap

There are two main guidelines in UK primary care for the referral and management of GCA, from NICE and the British Society of Rheumatology (BSR) (Mackie et al., 2020; NICE CKS, 2020). However, identifying patients in primary care when they present with GCA remains challenging for GPs, and as such there remains a long diagnostic delay for this medical emergency. Symptoms recommended as indicators of GCA in clinical guidelines, such as headache and jaw claudication, are used by GPs to determine GCA diagnosis, but these are only found within a proportion of cases, and therefore, relying on these individual indicators to identify every GCA case remains problematic.

Further research is required to determine the true extent of “classic” GCA symptoms, identify other symptoms, signs, comorbidities, and tests (clinical features) that could aid the

diagnosis of GCA in primary care, and explore how such clinical features may be co-occurring prior to primary care patients receiving a diagnosis of GCA.

Chapter 3: Clinical features prior to GCA diagnosis: a systematic review and meta-analysis

3.1 Chapter overview

As reported in Chapter 2, section 2.2.2, whilst several clinical features have been suggested to be associated with GCA in individual studies there has been no recent systematic synthesis of evidence across all studies on their prevalence and association with a diagnosis of GCA. This chapter describes the methods and findings of a systematic review and meta-analysis examining the prevalence and association of clinical features (i.e. symptoms, signs, comorbidities, and laboratory test findings) reported by patients prior to diagnosis of GCA.

3.2 Introduction

Chapter 2 highlighted that GCA can be difficult to clinically identify in primary care. This in-part can be because there is a wide range of reported clinical features for GCA. Many of these, such as fever or weight loss, may be commonly seen in primary care and can be attributed to other more prevalent conditions. GPs may also over rely on headache as an indicator of GCA, with its absence excluding the illness (Helliwell et al., 2018). Such issues may be a reason for diagnostic delay commonly occurring in GCA populations (Prior et al., 2017). Pooling available articles which have reported the clinical features experienced prior to a GCA diagnosis may aid in understanding what the most common presenting features of GCA are, and the extent of the role they have in any subsequent GCA diagnosis. Such information may contribute to greater diagnostic precision which can steer future guidelines for clinicians to reduce diagnostic delays, and inform future research studies.

Previous pooling of data on the clinical features with which GCA patients present prior to diagnosis, or associated with GCA diagnosis, is limited, with only one study having pooled available information on GCA symptoms (Smetana & Shmerling, 2002). The aim of this previous review was to investigate which clinical features would be predictive of a positive temporal artery biopsy (TAB), and therefore only articles where a TAB had been conducted were included. They used likelihood ratios to present their results, and found that tender temporal artery, weight loss, diplopia, any headache, and jaw claudication all had high predictive value of a positive TAB (Smetana & Shmerling, 2002). However, their review was conducted in 2000 was limited in the scope of its search by only using MEDLiNE and English language-only articles, and has not included the research into GCA conducted over the interceding decades.

The aim of the review reported in this chapter was to expand on the scope of the previous research by also including studies performed in the 17 years since that review was conducted, searching more bibliographic databases, performing a search with no English-language filter and not limiting to studies which only used temporal artery biopsy (TAB) as diagnostic confirmation. Whilst TAB is considered the gold standard diagnostic test for GCA and therefore maximising diagnostic precision of the review, it is considered to have poor sensitivity (Davies & May, 2011). Therefore, limiting a search to only TAB positive cases may limit the scope of the review, as TAB negative GCA patients would not have been included, potentially missing important, yet relevant findings. Although TAB is considered the gold standard method to confirm a diagnosis of GCA, there are studies which use recognised classification criteria, temporal artery ultrasound, electronic health record medical codes, and expert opinion.

3.3 Aims and Objectives

The aim of this systematic review was to identify from the literature clinical features that were reported in patient samples prior to their diagnosis of GCA. The specific objectives were:

1. To determine the prevalence of clinical features prior to GCA diagnosis.
2. To determine the strength of association between clinical features and subsequent diagnosis of GCA.

3.4 Methods

3.4.1 Overview

A systematic review of the current literature was conducted, with each stage including multiple reviewers. Articles were chosen based on pre-defined inclusion/exclusion criteria. Final inclusion of articles in the review were agreed by consensus and then required data extracted. Where possible, data was pooled using meta-analysis, followed by a meta-regression to investigate potential reasons for heterogeneity between studies.

3.4.2 Medical Databases

The bibliographical databases searched to identify articles for inclusion were Medline, Embase, CinAHL, and Web of Science. These databases were searched from inception to the date of search, on the 4th December 2017.

- MEDLINE: accessed via Ovid interface. This is a bibliographic database that includes literature published around the world from 1966 onwards. It covers a broad range of subject areas and has the ability to search for Medical Subject Headings (MeSH) terms. MeSH terms are a pre-defined list of medical labels that are used to describe

topics the article is linked to, used by the National Library of Medicine (Baumann, 2016). Within the MEDLINE database articles are linked to relevant MeSH terms, which allows for more efficient searching, and the avoidance of spelling differences (Baumann, 2016).

- Embase: accessed via Ovid interface. This biomedical, pharmacological, and pharmacovigilance database includes literature from 1947 onwards, and has over 32 million records available. MeSH terms are also available to be searched, giving a broader range to search strategies.
- CiNAHL: CINAHL is a nursing literature database aimed at all medical practitioners, but with a nursing specialities focus. With some full-text articles available as far back as 1937, this covers a wide range of relevant journals.
- Web of Science: is a collation of databases that includes MEDLINE. Since MEDLINE was already searched separately only core databases, such as Science Citation Index Expanded and Social Sciences Citation Index, in Web of Science were included. There are more than 12,000 journals available to search through this database ranging from social sciences to humanities.

These databases were searched because they were the largest and most relevant bibliographic databases available at the time of the review, have been used in previous reviews on GCA (Hill et al., 2017; Smetana & Shmerling, 2002), and effectively cover all aspects of GCA care and research.

A protocol for the systematic review was created to ensure all key aspects were planned prior to commencement. This protocol was then internally reviewed by the host department's (School of Medicine) systematic review team and once finalised was registered with PROSPERO (registration number: CRD42018083411) in January 2018 (Appendix 3.1).

PROSPERO is a database, hosted by the National Institute of Health Research (NIHR) in collaboration with the University of York that collates systematic reviews which have a health-related outcome. Systematic reviews are registered with PROSPERO at inception, or at the start of database searching, so as to avoid duplication between different research teams, and prevent reporting bias by allowing the protocol and finished review to be compared (University of York, 2020).

3.4.3 Inclusion criteria

To be included in the review, articles had to have:

1. GCA diagnosis confirmed by at least one of the following methods:
    a. The American College of Rheumatology classification criteria (Gene G. Hunder et al., 1990)
    b. A positive temporal artery biopsy
    c. A qualified medical expert
    d. A medical code for GCA in the patient's record such as a Read code (a hierarchical structure of codes that record diagnoses, tests and other information regarding the patient's record in UK primary care), or ICD-10 code (a coding system used in UK secondary care).
    e. A patient self-reported diagnosis of GCA.
2. Reported any clinical feature(s) with which the samples had presented pre-diagnosis of GCA.
3. A report of either the prevalence of the clinical feature(s), a measure of association for the clinical feature with a diagnosis of GCA, or both.

There was no restriction on type of healthcare or study design from which samples were extracted. Articles could:

1. Be conducted in primary, secondary, or tertiary care
2. Use any of the following study designs:
    a. Cohort (when patients are selected based on exposure)
    b. Case-control (where patients are selected based on outcome)
    c. Randomised control trial (where patients with a condition are randomised to two or more treatment groups and followed up for a set amount of time to see if they improve)
    d. Cross-sectional (when patients are investigated at a specific point in time).

Articles were not excluded based on language, with the view to translate them at full-text review if they were retained to that stage of the process. The translation would be conducted using the in-house translation services.

3.4.4 Exclusion criteria

Articles were excluded from the review based on the following specific criteria:

1. If the study was focused on clinical features reported post-diagnosis of GCA.
2. If the study contained no original data, i.e. literature reviews, editorials, systematic reviews, and meta-analysis.
3. If the study was conducted on human tissue, such as gene research, or laboratory-based research, or on non-human subjects.
4. Case report, case studies, or case series.
5. If the study was focused on evaluating or comparing a method of diagnosis, such as temporal artery biopsy, colour ultrasonography, etc.

6. If the study focused on PMR as a condition with GCA as a comorbidity.

3.4.5 Search Strategy

3.4.5.1 Initial identification of clinical features

Prior to searching the four selected bibliographic databases, a scoping review was conducted on general databases, such as PubMed and Google Scholar, to identify suitable clinical features to build the formal search strategy for the review. This involved searching for general terms, such as GCA, and appraising articles that were relevant, along with their reference lists (Table 3.1).

Table 3.1: Clinical features identified through scoping exercise.

Clinical feature included in systematic review search strategy	**Reference where clinical feature identified**
PMR	Smetana et al. (2002); Hassan et al. (2011); Salvarani et al. (2008)
Visual disturbances - all	Smetana et al. (2002); Barraclough et al (2012); Hassan et al. (2011); Salvarani et al (2005)
Infections - all	Russo et al (1995); Falardeau et al. (2010)
Headache - all	Smetana et al. (2002); Barraclough et al (2012); Hassan et al. (2011); Prior et al. (2017)
Abnormal temporal artery/scalp tenderness	Barraclough et al (2012); Yates et al. (2016); Prior et al (2017)
Jaw/tongue claudication	Smetana et al. (2002); Hassan et al. (2011); Barraclough et al. (2012); Prior et al. (2017)
Weight loss	Smetana et al. (2002); Falardeau et al. (2010); Hassan et al. (2011); Barraclough et al. (2012); Yates (2016)
Fever	Smetana et al. (2002); Barraclough et al. (2012)
ESR	Hassan et al. (2011); Barraclough et al. (2012)
Cardiovascular/cerebrovascular conditions	Mackie et al. (2011); Tomasson et al. (2014); Saleh et al. (2016)
Diabetes	Mackie et al. (2011); Falardeau et al. (2010); Saleh et al. (2016)
Osteoporosis	Petri et al. (2015); Sozen et al. (2017)
VTE	Saleh et al. (2016); Lin et al. (2017)
Falls	Petri et al. (2015); Al-Aama (2011)
Asthenia	Salvarani et al. (2005); Gonzalez-Gay et al. (2015)
Musculoskeletal conditions/symptoms	Falardeau et al. (2010); Petri (2015)
Atherosclerosis	Mackie et al. (2011); Saleh et al. (2016)
Aortic aneurysm	Evans et al. (1995); Dejaco et al. (2017); Falardeu et al. (2010)

ESR - erythrocyte sedimentation rate; VTE - Venous thromboembolism; PMR - Polymyalgia Rheumatica; Asthenia – lack of energy or strength.

3.4.5.2 Development of search strategy

MEDLINE, Embase, CiNAHL, and Web of Science were all searched. The search strategy for each database is outlined in Appendix 3.2. Strategies differed little between MEDLINE and Embase, and included MeSH terms where possible. The “explode” option for MeSH terms was added to the search strategy for CINAHL, where available, since this has the capability to search for all associated terms, such as synonyms for stroke, aortic aneurysm, and diabetes. The “classical” features of GCA, such as headache, PMR symptoms, and visual disturbances, which have been established in the literature (Dasgupta et al., 2010), were included in the search strategy. These were expanded to include the type of headache (temporal, frontal, etc.), and type of visual disturbance (complete, transient or permanent loss, blurred vision, etc.).

Other features, for example, jaw claudication, scalp tenderness, fever, and weight loss were added based on the scoping literature search. Infections, such as urinary tract infections were included after being found to have been investigated in a number of studies (Falardeau, 2010; Russo, Waxman, Abdoh, & Serebro, 1995). There was no minimum number of studies in which a clinical feature was reported to warrant its inclusion in the search criteria. Features common in an elderly population such as falls, the wide term of “musculoskeletal conditions", and osteoporosis were also included. The laboratory based measurement ESR was also included since this has been assessed in a number of studies (Barraclough et al., 2012; Hassan et al., 2011).

Titles and abstracts of articles were searched using the final search strategy. The resulting citations from all databases were exported and entered into Refworks (ProQuest, Version 2018), a reference managing software system available online (ProQuest, 2020). Before title screening began, exact duplicates were removed using the function within Refworks, this

software was only used for title screening due to its superior ability to remove duplicate articles. Remaining articles were then moved to Mendeley (V1.17.11), a citation software (Elsevier, 2020), similar to Refworks, to continue the filtering process.

3.4.6 Article screening process

One reviewer (Lauren A. Barnett (LAB)) screened all titles. If an article title failed to meet any of the exclusion criteria it was kept for abstract review. Two reviewers (LAB and Chris Morton (CM)) then independently screened the remaining articles by abstract. Any article kept by either reviewer (LB or CM) was moved through to full-text review. These articles were reviewed by a single reviewer (LAB), with a third of articles completed by two independent reviewers (Alyshah Abdul-Sultan (AAS), and James Prior (JAP)). At full-text review stage, reference lists of included papers were searched by LAB for further relevant studies to include in the final review and analysis.

3.4.7 Quality assessment

It is important to assess the quality of articles included in any systematic review (Moher et al., 1999). Systematic reviews should always aim to reduce bias of the eventual conclusions by reviewing literature in a systematic and logical way (Moja et al., 2005). Conducting a quality assessment on individual studies included in a systematic review indicates how strong the conclusions of that study are (Seehra, Pandis, Koletsi, & Fleming, 2016).

To assess the quality of the studies included in this review, the Newcastle-Ottowa (N-O) scale for cohort, and case-control studies was used. Any cross-sectional studies were assessed using the case-control Newcastle-Ottowa scale (Luchini, Stubbs, Solmi, & Veronese, 2017).

Each question on the Newcastle-Ottowa scale is given a star rating dependent upon the answers, for both the cohort and case-control studies. For instance the “Representativeness of cohort” question in the cohort scale has four possible answers; “truly”, “somewhat”, “of selected group of users”, or “no description”. Stars are only allocated to the “truly” and “somewhat” answer categories. Articles of cohort studies which received between zero and one star (out of a maximum of seven stars) were rated as poor quality. Articles which had two or three stars were fair quality, and articles which had three stars or more were good quality. For the case-control studies zero or one star defined poor quality, two stars indicate fair quality, and three or four stars indicate good quality (Wells et al., 2019).

For trials that reached the full text review stage, the Cochrane Collaboration tool for assessing bias would be used. This is a tool developed in 2008 and updated in 2011 that assesses the risk of bias in randomised controlled-trials based on seven criteria (Jørgensen et al., 2016). Quality assessment of all included studies was conducted by LAB.

3.4.8 Data extraction

Data extraction from included studies was conducted by LAB based on a created data extraction form (Appendix 3.3, Table 1). This was used to collect information on study setting, country and continent of study origin, gender distribution of study population, method of GCA diagnosis, length of retrospective/prospective follow-up, reported clinical feature, duration of clinical feature prior to diagnosis, the percentage of confirmed GCA patients reporting features (i.e. prevalence) and any estimate of association reported (derived from raw data, or a reported unadjusted or adjusted estimate). If any required data was not reported in the articles, then the corresponding author was contacted and asked to share the appropriate data. Where the prevalence was already reported in an article, this

was used as the estimate. Where it was not stated in the article, the proportion of patients in the study population who reported the clinical feature prior to their GCA diagnosis (n) and the total study population (N) was extracted from each article. The prevalence estimates were calculated by n/N. The number of patients with GCA and who did (a) and did not (c) experience the clinical feature, and non-GCA patients who did (b) and did not (d), was extracted and the risk estimate (unadjusted odds ratio) was calculated by ad/bc for all relevant articles.

3.4.9 Narrative synthesis

A narrative synthesis was conducted on the articles included in the final review. A narrative synthesis is a method of summarising and synthesising data from a review using text. It is predominately used prior to a meta-analysis, or in lieu of one when there is not sufficient studies or data to complete a formal quantitative analysis. Study characteristics were compared and critically appraised. These clinical features were synthesised, with the sample size, study quality, setting, and estimates associated with the clinical feature compared between included articles. The design of the study was reported, along with the type of diagnosis of GCA used in the article. Any possible differences in estimate size or direction of association between articles was also discussed.

Clinical features which affected the same biological system were grouped together where numbers of articles were low, for ease of comparison. Visual symptoms included all variations of sight loss (transient, permanent, etc.), double vision, blurred vision, and field loss. Cardiovascular/cerebrovascular diseases included: arterial hypertension and coronary artery disease, myocardial infarction, stroke, atrial fibrillation, transient ischaemic attacks, and congestive heart failure. Systemic/constitutional symptoms were defined as one or

more of fatigue, fever, weight loss, night sweats, dizziness, anorexia, malaise, and asthenia. Mental health manifestations included psychiatric disorders (undefined), dementia, and mental deterioration. Anorexia was interpreted as loss of appetite, so as to separate it from weight loss.

Originally reported values which pertained to the presence or absence of a clinical feature were retained, where stated in an article (e.g. the presence of a fever determined by a temperature above 38 degrees Celsius).

3.4.10 Meta-analysis

There are two possible methods of meta-analysis available; fixed effect and random effect. In recent years, random effect meta-analyses have been recommended as generally the most appropriate (Riley, Higgins, & Deeks, 2011). A random effects meta-analysis assumes that effect size (for example, odds ratio relating to association of a clinical feature with GCA) varies between studies due to reasons other than chance, as opposed to fixed effects meta-analysis which assumes any differences in effect size between studies is entirely due to chance (Riley et al., 2011). Heterogeneity in effect size may occur because of differences in demographics, sample size, study design, or follow-up time, between studies. In the case of fixed-effects meta-analysis, since it assumes the effect size is the same, from the largest to the smallest study, it tends to assign a smaller weight to the small studies since the same study information about the effect size can be found in the larger studies (Borenstein, Hedges, Higgins, & Rothstein, 2010). In the random-effects models the weight of each study is determined by the within-study variance (Borenstein et al., 2010). Often, fixed-effects meta-analysis is not plausible as all studies will not have the same underlying effect size, due to factors such as study design rather than chance (Borenstein et al., 2010). The

interpretation of differences between fixed and random effects meta-analysis is that in fixed effects the meta-analysis provides the best estimate of an effect that is assumed to be constant across all studies. However, in random effects meta-analysis the results show the average effect from the distribution of effects across all studies (Riley et al., 2011).

Random-effects meta-analyses were conducted on the prevalence and association data for each reported clinical feature. The Freeman-Tukey double arcsine method is recommended to transform the prevalence estimates reported in studies with small sample sizes prior to conducting a meta-analysis. This method normalises the variance and sampling distribution of the prevalence estimates (Freeman & Tukey, 1950), the estimate is then back transformed (Miller, 1978).

For the meta-analyses pooling estimates of association, only the articles that had a control population could be included. Controls were defined to be either the general population without disease, or temporal artery biopsy-negative patients. Odds ratios were calculated from the raw data (for example, biopsy positive, biopsy negative, clinical feature present, and clinical feature not present) irrespective of if the article reported one. Only unadjusted odds ratios were extracted since covariates were not consistent across all articles or not stated in the methods. Articles that only examined GCA positive cases could not be included in this meta-analysis since there was no comparison, or "control" group, where the risk estimate could be calculated.

Meta-analysis has heterogeneity, relating to the uniformity between data, typically between the effect sizes of each article (Sedgwick, 2015). There are commonly two sources of variability that would explain heterogeneity (Huedo-Medina, Sanchez-Meca, Marin-Martinez, & Botella, 2006). The first is "within-study" variability, defined as variability due to

sampling error, and the other is "between-study" variability, defined as differences in effect-sizes between studies (Huedo-Medina et al., 2006).

Heterogeneity of the prevalence estimates and estimates of association was reported using the I^2 statistic and the τ^2 statistic. The I^2 is the proportion of variation between the estimates that is due to variability among studies, rather than sampling error (Huedo-Medina et al., 2006). It is given by the following formula:

$$I^2 = \frac{Q - (k-1)}{Q} \quad (1)$$

Where:

$$Q = \sum w_i \left(y_i - \frac{\sum w_i y_i}{\sum w_i} \right)^2$$

Assuming there are *k* studies, w_i is the weight of study *i* (i = 1...k), and y_i is the effect size in that study. I^2 takes values between 0% and 100%, with general categorical cut-offs at 25% for low, 50% for moderate, and 75% for high heterogeneity (Sedgwick, 2015). An advantage of I^2 is that it is not reliant on the number of studies included in the meta-analysis, unlike other available measures of heterogeneity (Sedgwick, 2015). However, I^2 increases as the precision, proportional to the sample size, of the studies included in the meta-analysis increase. This can be illustrated in the interpretation of I^2. Since it is the amount of heterogeneity due to between-study variability, its inverse 1-I^2 is the variability due to sampling error. As the sampling error becomes smaller, I^2 becomes larger (Rücker, Schwarzer, Carpenter, & Schumacher, 2008). Therefore, I^2 increases as the sample size of included studies increases, and hence has its limitations as a measure of true heterogeneity. In contrast to I^2, the τ^2 describes the underlying between-study variability, and is calculated by;

$$\tau^2 = max\left\{0, \frac{Q-(k-1)}{\sum w_i - \frac{\sum w_i^2}{\sum w_i}}\right\} \quad (2)$$

Q is Cochrane's Q-statistic defined as above, *k* is the number of studies in a meta-analysis, and w_i is the weight of study *i* (*i* = 1,…*k*). This measure does not increase with the number of studies in the meta-analysis, or the precision of the studies (Rücker et al., 2008), therefore it is a more stable estimate of heterogeneity than I^2. It can take values from 0 to ∞, and the larger the value it takes the more heterogeneity is present in the meta-analysis. There is currently no recommended cut-off value for high heterogeneity for τ^2. Both I^2 and τ^2will be reported in this review.

There will be variability around the pooled estimates from the meta-analysis. This will be illustrated using 95% confidence intervals, and 95% prediction intervals. The confidence interval gives a range of values where the true estimate (prevalence or risk) can lie (Riley et al., 2011). The wider the confidence interval, the greater the uncertainty surrounding the estimate.

However, prediction intervals have been advocated for reporting in systematic reviews in addition to confidence intervals (Riley et al., 2011). These can give a range where the predicted estimate of a new study is likely to lie rather than a range where the current estimate can lie. This future study would have to be of a similar design to the ones used in the meta-analysis for the predicted range to be valid (Higgins, Thompson, & Spiegelhalter, 2009). Despite the usefulness of prediction intervals they are rarely reported in published meta-analyses, which instead choose confidence intervals which are more frequently reported in published articles (Riley et al., 2011). For this reason both the confidence intervals and prediction intervals will be reported in this review.

Pooled estimates, measures of heterogeneity, confidence intervals, and prediction intervals were all calculated and added to a forest plot. A forest plot is a method of visualising the individual study and pooled estimates from a meta-analysis.

As data on both the prevalence and association of a clinical feature was extracted through the systematic review, one meta-analysis pooled together the prevalence estimates in the study population, and another pooled the estimates of association for each clinical feature. Meta-analysis was not conducted on clinical features reported in less than three articles. Currently, there is no set guidance about the minimal number of articles that should be included in a meta-analysis, but three is the recommended minimum required to calculate a prediction interval (Riley et al., 2011), and a previously published systematic review and meta-analysis on diagnostic delay in GCA also used three as the minimum number of articles for a meta-analysis (Prior et al., 2017).

Random-effects meta-analyses were conducted on the data for each reported clinical feature, and where possible, further stratified by the point at which the feature was recorded prior to GCA diagnosis (for example recording when GCA was diagnosed, when temporal artery biopsy was taken, when patient was referred for GCA). This review aimed to find clinical features that were indicative of a GCA diagnosis. The association between a clinical feature and a GCA diagnosis may differ depending on when the clinical feature was recorded, i.e. at diagnosis, or 3 months prior. Hence why the subgroup analysis, stratified by point at which clinical feature was recorded, was conducted. All analyses were conducted using R version 3.4.1 (R Foundation for Statistical Computing, 2020).

3.4.11 Meta-regression

Meta-regression can be used to investigate the cause of any amount of heterogeneity in a pooled analysis, but it is more efficiently used in the cases where there are large amounts of heterogeneity that may be caused by multiple variables (Thompson & Higgins, 2002). When there were ten or more articles reporting prevalence of the clinical feature or the association of the clinical feature and a diagnosis of GCA, and there was heterogeneity over 80% (Thompson & Higgins, 2002) in the estimates, a meta-regression was conducted on available data to further investigate the cause of any heterogeneity.

A meta-regression is a form of modelling that attempts to explain the heterogeneity observed between studies included in a meta-analysis (Thompson & Higgins, 2002). It is conducted on article-level data, as opposed to regression analyses which are conducted on patient-level data (Thompson & Higgins, 2002). The independent variables of the models performed in this review were the study characteristics, and the outcome variable is the effect size measured for the meta-analysis, in this case prevalence or estimate of association of the clinical feature (Israel & Richter, 2011). To compare the fit of models including different covariates, the coefficient of determination (R^2) was reported. The R^2 value is a model fit statistic that explains how much variation in the data that the fitted model explains, and is mainly used to identify models with good fit (Asuero, Sayago, & González, 2006), taking values from 0% to 100%. The higher the percentage the better the model fit.

Data extracted from the articles included in the review were used as the independent variables in the meta-regression analysis. There were no *a priori* hypotheses about the source of heterogeneity prior to the analysis, hence all extracted variables from the review were used as covariates. Only articles where the clinical features had been recorded at

diagnosis/TAB were included in the meta-regression, since the scoping search suggested this would be the largest group. The variables that were included in the meta-regression were:

1. Continent of study origin - a categorical variable; divided into Americas (reference category), Europe, and Other (Africa, Oceania, and Asia).
2. Study quality – based on the Newcastle-Ottowa scale categorised into the 3 levels defined by the authors who developed the tool (Wells et al., 2019), good (reference category), fair, and poor.
3. Study design – categorised into 2 levels (originally 4 to include trials and crossover studies); case-control (reference category) and cohort.
4. Proportion of females in the study population – a continuous variable indicating the percentage of patients in the study population that were female.
5. Year of publication – a categorical variable with 3 levels; 1970-2000 (reference category), 2001-2010, and 2011-present.
6. Mean age – a continuous variable.
7. Method of GCA diagnosis – categorised into 4 levels, TAB (reference category), ACR, ACR/TAB, and "other". "Other" included criteria that was not ACR/TAB, or medical codes such as ICD-10.

A univariable model was fitted initially for each independent variable. The covariates from the univariable models with the largest R^2 value were then added together to a multivariable model to see if this would improve the amount of heterogeneity explained.

3.5 Results

3.5.1 Database searches

A total of 10,192 articles were identified in the initial search; 2611 duplicates were identified and removed, resulting in 7581 unique titles for review. 6992 articles were excluded through title screening as they did not meet the inclusion criteria, leaving 589 abstracts for review. Of these, 66 could not be sourced (due to the journals in which they were published having no archive access), 262 were excluded due to study design, and 171 did not meet the inclusion criteria detailed in section 3.4.3. A total of 90 articles were identified for full-text review. Of the 90 full-text articles that were reviewed independently, 4 were found to be duplicates, 7 were unavailable as full-text articles (because no UK library could access a copy), and 41 did not meet the inclusion criteria, leaving 38 articles. A further 5 studies were added after a manual reference list search of the 38 articles, giving a total of 43 studies (35 reporting prevalence estimates, and 18 reporting association estimates) included in the systematic review for quality assessment, data extraction, and analysis (Figure 3.1).

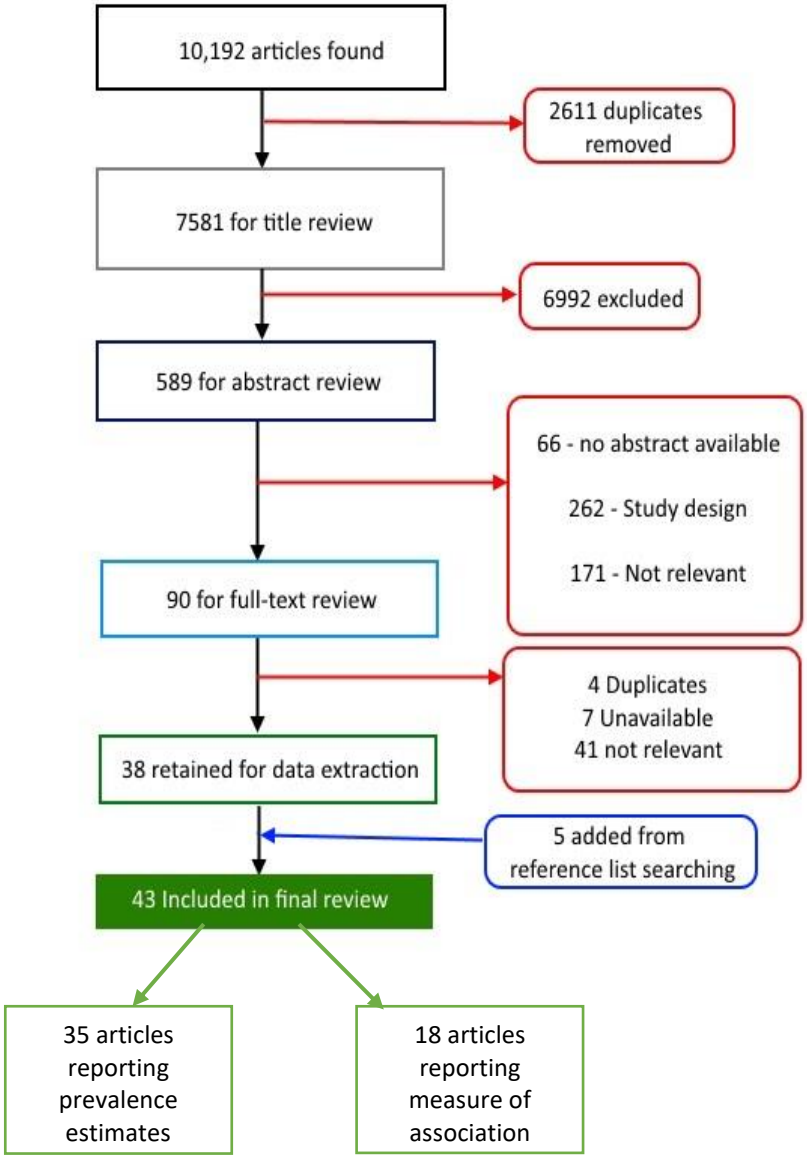


Figure 3.1: Flowchart of articles included in review.

3.5.2 General characteristics of included articles

Articles included in the review were published between 1979 and 2017 (
Table 3.2). The most common study design was cohort (n = 38), whilst the remaining studies were case-control design (n = 5). No cross-sectional studies or trials were identified. Cohorts were either retrospective (89.5%) or prospective (10.5%). In the case of retrospective articles these were usually conducted by a medical record review in one or more secondary/tertiary care departments. In these instances, authors determine patients who had been diagnosed with GCA within a certain time-period and extract healthcare data from their records and report what clinical features they had presented with prior to diagnosis. In the case of prospective cohorts, the authors would determine patients who had been diagnosed with GCA within a certain time period and summarise the clinical features they had reported at their diagnosis before following the patient's forwards.

Three articles were based in the UK. The most common country of sample origin was the USA (n = 14), followed by Spain (n = 6). Only one article included in the review required translation as this was written in Spanish (Rivero Puente et al., 2001). Only one article in this review used a national electronic health records (EHR) database (Unizony et al., 2017), the rest were record reviews conducted in secondary/tertiary care departments.

The minimum overall sample size (all subjects recruited to the study, regardless of GCA status) was 22 (Espitia et al., 2012), whilst the maximum was 6414 (Unizony et al., 2017). The median sample size was 116. The period in which cases were identified varied between studies, with the shortest being during a 6 month period (Fainaru, Friedman, & Friedman, 1979), and the longest was a population cohort where cases were identified from 1950 to 2004 (Abha G. Singh et al., 2015).

The highest proportion of female patients in the study samples was 82% (Alba, Mena-Madrazo, Reyes, & FloresSuarez, 2011), whilst the lowest was 50% (Sun et al., 2016). There were six articles that reported no information on the proportion of females in the study sample. Age of the samples was similar between studies, with most articles reporting on patients aged over 50 years. The highest mean age reported was 76.1 years (Garrity et al., 2017), whilst the lowest was 66.4 years (Sun et al., 2016). Eleven articles did not report the age of the study sample.

3.5.3 Quality assessment

The majority of the articles included were of fair quality (n = 27). Only 2 articles were of poor quality (Rivero Puente et al., 2001; Sun et al., 2016). The remaining articles were of good quality. The elements of the N-O scale where these articles rated poorly were representativeness of cohort, and selection of comparison group. Neither article had a comparison group since all patients included had been diagnosed with GCA. Both articles were single-centre only (

Table 3.2).

Table 3.2: Extracted information for all articles in the review.

First author	Year	Study design	Country	Quality	Healthcare setting	GCA diagnosis	Length of sampling period (years)	Time feature was reported	Total sample size	Gender (%F)	Mean age (years)	Age range (years)
Alba	2011	Retrospective cohort	Mexico	Fair	Secondary	ACR/TAB	21	At diagnosis/TAB	22	82.0	73.0	57-84
Chmelewski	1992	Retrospective cohort	USA	Fair	Secondary	TAB	5	At diagnosis/TAB	98	68.4	73.1	56-93
de Boysson	2016	Retrospective cohort	France	Good	Secondary	ACR criteria	10	At diagnosis/TAB	143	66.0	NA	50-86
Desmet	1990	Retrospective cohort	Belgium	Fair	Secondary	clinical or histological	6	At referral to secondary care	82	73.5	70.0	60-99
Duhaut	1999	Prospective cohort	France	Good	Secondary	ACR & TAB	6	At diagnosis/TAB	292	72.9	74.9	NA
Dunstan	2014	Prospective cohort	South Australia	Fair	Pathology lab	TAB	19	At diagnosis/TAB	314	72.0	NA	NA
El-Dairi	2015	Retrospective cohort	USA	Fair	Secondary	TAB	9	At diagnosis/TAB	204	71.0	75.0	54-90
England	2017	Retrospective cohort	USA	Good	Medical & pharmacy claims data	ICD-9-CM code	8	At diagnosis/TAB	5942	NA	NA	NA
Espitia	2012	Retrospective cohort	France	Fair	Secondary	TAB & ACR	13	At diagnosis/TAB	22	NA	NA	NA
Ezeonyeji	2010	Retrospective cohort	UK	Fair	Medical records	Rheumatologist	5	average 35 days	65	NA	NA	NA
Fainaru	1979	Retrospective cohort	Israel	Fair	Secondary	TAB	0.5	At diagnosis/TAB	47	55.3	69.4	60-84
Gabriel	1995	Prospective cohort	USA	Fair	Secondary	TAB	3	At diagnosis/TAB	525	64.0	72.5	NA
Garrity	2017	Retrospective cohort	USA	Fair	Any	TAB	10	At diagnosis/TAB	32	69.0	72.6	46-91

First author	Year	Study design	Country	Quality	Healthcare setting	GCA diagnosis	Length of sampling period (years)	Duration of features prior to diagnosis	Total sample size	Gender (%F)	Mean age (years)	Age range (years)
Garrity	2017	Retrospective cohort	USA	Good	Any	TAB	10	At diagnosis/TAB	84	71.0	76.1	57-93
Gonzalez	1989	Retrospective cohort	USA	Fair	Secondary	TAB & defined criteria	10	At diagnosis/TAB	27	77.8	NA	NA
Gonzalez-Gay	2001	Retrospective cohort	Spain	Fair	Secondary	TAB	17	At diagnosis/TAB	190	50.9	74.8	NA
Gonzalez-Gay	2004	Retrospective cohort	Italy & Spain	Fair	Secondary	TAB	15	At diagnosis/TAB	320	61.9	74.2	NA
Gonzalez-Gay	2005	Retrospective cohort	Spain	Good	Secondary	TAB	23	At diagnosis/TAB	240	54.2	75.0	NA
Gonzalez-Lopez	2013	Case-control	Spain	Good	Secondary	TAB	9	At diagnosis/TAB	335	65.7	74.2	NA
Grossman	2016	Retrospective cohort	Israel	Fair	Medical centre	TAB	14	At diagnosis/TAB	224	66.0	73.0	NA
Haugeberg	2000	Retrospective cohort	Norway	Fair	Secondary	ICD codes & TAB	4	At diagnosis/TAB	53	71.7	72.7	NA
Hayreh	1997	Prospective cohort	USA	Good	Any	TAB	21	At referral to secondary care	363	66.1	72.0	20-95
Kermani	2012	Retrospective cohort	USA	Fair	Secondary	TAB	8	At diagnosis/TAB	764	73.4	74.5	NA
Khalifa	2009	Retrospective cohort	Tunisia	Fair	Secondary	ACR/TAB	17	At diagnosis/TAB	96	53.0	70.8	50-91
Kobayashi	2003	Questionnaire	Japan	Good	Secondary	ACR	1	At onset of illness	66	63.6	72.5	49-92
Lugo	2011	Retrospective cohort	USA	Good	Secondary	TAB	7	At diagnosis/TAB	138	76.0	74.0	NA
Machado	1988	Prospective cohort	USA	Good	Medical records	TAB, and other criteria	35	At diagnosis/TAB	94	NA	NA	NA
Mari	2009	Retrospective cohort	Spain	Fair	Secondary	TAB	18	At diagnosis/TAB	278	65.1	74.8	59-89

First author	Year	Study design	Country	Quality	Healthcare setting	GCA diagnosis	Length of sampling period (years)	Duration of features prior to diagnosis	Total sample size	Gender (%F)	Mean age (years)	Age range (years)
Mohamed	2002	Retrospective cohort	UK	Fair	Secondary	TAB	9	At diagnosis/TAB	51	71.0	69.5	19-85
Myklebust	1996	Prospective cohort	Norway	Fair	Secondary	ACR	7	At diagnosis/TAB	335	74.4	70.4	NA
Narveaz	2003	Retrospective cohort	Spain	Fair	Secondary	ACR/TAB	14	At diagnosis/TAB	73	67.0	72.0	51-89
Nesher	1996	Retrospective cohort	Israel	Good	Secondary	ACR	12	At diagnosis/TAB	91	66.0	NA	60-80
Pugnet	2015	Case-control	France	Poor	Medical records	ICD-10 code	6	>1 month before diagnosis	103	77.7	74.8	51-91
Rivero-Puente	2001	Retrospective cohort	Spain	Good	Secondary	TAB	9	At diagnosis/TAB	57	52.6	72.7	56-85
Roth	1984	Retrospective cohort	USA	Fair	Secondary	TAB	16	At diagnosis/TAB	51	71.0	76.1	61-97
Russo	1995	Case-control	USA	Fair	Medical records	TAB	NA	average 60 days	200	81.0	70.5	48-88
Salvarani	1999	Secondary analysis	USA	Fair	Any	ACR criteria/TAB	41	>2 months before diagnosis	128	NA	NA	NA
Silva de Souza	2013	Retrospective cohort	Brazil	Fair	Tertiary	ACR	1	At onset of illness	45	64.4	NA	NA
Singh	2015	Retrospective cohort	USA	Good	Medical records	ACR	54	At diagnosis/TAB	204	80.0	76.0	NA
Stuart	1989	Retrospective cohort	New Zealand	Poor	Secondary	TAB	4	At diagnosis/TAB	75	79.0	NA	50-88
Sun	2016	Retrospective cohort	China	Fair	Secondary	ACR criteria/TAB	22	At diagnosis/TAB	70	50.0	66.4	NA
Toren	2016	Prospective cohort	Canada	Good	Secondary	TAB	3	At diagnosis/TAB	250	70.0	73.7	58-95
Unizony	2017	Retrospective cohort	UK	Fair	Medical records	GCA code & steroid prescription code	23	≤12 months before diagnosis	6414	70.0	73.0	NA
Zenone	2013	Prospective cohort	France	Fair	Secondary	ACR	11	At referral to secondary care	88	67.0	74.9	59-92

3.5.3.1 Definition of a GCA diagnosis

Almost half of the articles used temporal artery biopsy (TAB) as the method of GCA diagnosis (n = 21), followed by the ACR classification (n = 6). Articles that were published prior to 1990, when the ACR classification criteria were published, often created their own criteria for study inclusion, which were generally similar to the ACR criteria (n=7).

3.5.3.2 Duration of clinical features prior to diagnosis

The majority of articles did not state the duration of clinical features reported by patients prior to a GCA diagnosis. Only 5 articles reported length of exposure period, and all differed. Two articles reported average durations of 35 days and 2 months prior. The remaining three included features that had been experienced by patients for more than 1 month prior, more than 2 months prior, and less than or equal to 12 months prior.

Thirty-three articles recorded features present at diagnosis or at temporal artery biopsy, and gave no further information on duration. Information on clinical features was taken from internal medical records. Three articles recorded patient features at time of referral to secondary care, but no further information was available as to how long a patient waited to be seen in secondary care. The remaining two articles contained features that were present at disease onset, with no information on how long this time was before diagnosis.

3.5.3.3 Clinical features examined in included studies

A total of 50 different clinical features, which GCA patients presented with before GCA diagnosis, were examined in these studies. The clinical features most frequently examined in studies were headache (n = 35), jaw claudication (n = 32) and PMR (n = 32). All articles reporting headache gave the proportion of patients presenting with overall or general

headache of recent onset, whilst one also gave numbers for more specified types, such as temporal and occipital (Souza et al., 2013). Visual impairment (excluding diplopia, which was reported in eight articles hence enough for a separate meta-analysis) was reported in 31 articles. However, the majority of these articles simply defined this as visual impairment, disorders, symptoms, disturbances, or manifestations, with little detail about what these included.

Some studies did include detail about cut-offs used to define clinical features. Elevated ESR (n = 8) was defined as >50 mm/h in four articles (El-Dairi et al., 2015; Marí et al., 2009; Mohamed & Bates, 2002; Rivero Puente et al., 2001), >40 mm/h in one article (E. B. V Machado et al., 1987), >100 mm/h in one article (Chmelewski et al., 1992), and was undefined in two articles (T.A. Kermani et al., 2012; Toren et al., 2016). Where weight loss pre-GCA diagnosis was examined (n = 17), only four articles actually defined a value for weight loss. Three defined it as >10% loss within six months (Alba et al., 2011; Duhaut, Pinède, et al., 1999; A.G Singh et al., 2015) and one article (Desmet et al., 1990) defined it as >2kg loss in two weeks, or >5kg loss over no specified time period. Fever (n = 26) was defined in two articles as >38 degrees Celsius (Gabriel et al., 1995; M.A. Gonzalez-Gay et al., 2005). One article defined it as >100 degrees Fahrenheit (Abha G. Singh et al., 2015). The remaining articles did not define a cut-off value for fever.

3.5.4 Infrequently reported clinical features

Cancer was only reported in two articles (Table 3.3). The two articles (Pugnet et al., 2015; Unizony et al., 2017) reporting cancer found that 9.7% and 12.6% of GCA patients respectively had (unspecified) cancer prior to their diagnosis. The article by Pugnet et al. (2015), conducted in France, included 103 GCA cases compared to 606 controls taken from

the general population. This case-control study used data from the French National Health Insurance (FNHIS) database (Pugnet et al., 2015). This covers more than 95% of the French population, hence the population in this study is likely to be generalizable. Unizony et al. (2017) used the Health Improvement Network (THIN) for their study which includes medical records for 10.2 million patients in the UK (Unizony et al., 2017). They used a matched cohort with cases having new-onset GCA each matched to 10 controls taken from the rest of the population, and with no diagnosis of GCA. This study included 6414 cases of GCA and was rated "Good" on the quality scale.

An article by Russo et al. (1995) reported different infections in patients up to four months prior to their diagnosis of GCA (Russo et al., 1995). Three other articles also reported infections, but due to none reporting the same infection this was not included in the meta-analyses reported below. Russo's findings for any infection in GCA patients prior to their diagnosis, which included any of the 13 infections investigated, was 63.0% of patients. The most commonly reported infection in this sample was urinary tract. Gabriel et al. (1995) reported 5.8% of GCA patients had been diagnosed with synovitis prior to their diagnosis, recorded at the time of diagnosis (Gabriel et al., 1995). England et al. (2017) found that the uncomplicated strain of herpes zoster was more prevalent than the complicated strain, but was only found in 3.0% of patients prior to a diagnosis of GCA, recorded at the time of diagnosis (England et al., 2017).

Night sweats were reported in two articles (Haugeberg, Paulsen, & Bie, 2000; Myklebust, Gran, & G., 1996), both conducted in Norway. Myklebust et al. (1996) conducted a prospective cohort study in south Norway, following patients until cessation of treatment for GCA. Only histologically proven cases of GCA were included in the study. A total of 39 patients were found to have GCA, of which 74.4% were female. Of the 39 patients included

in the study, 10 reported night sweats prior to a diagnosis of GCA (Myklebust et al., 1996). Haugeberg et al. (2000) used secondary care medical records (hospital records and a biopsy database) to identify GCA patients over a period of 4 years in southern Norway. The final sample size of GCA patients was 53, of which only four of these had reported night sweats prior to diagnosis.

Table 3.3: Clinical features of GCA prior to a diagnosis, reported in 2 articles or less.

Clinical feature	Author(s)	Year	Total number of GCA cases	Clinical feature present (N)	Clinical feature present (%)
Asthenia	Duhaut	1999	207	171	82.61
Asthenia	Sun	2016	70	33	47.14
Aortitis	Zenone	2013	88	5	5.68
Appetite loss	Dunstan	2014	88	37	42.05
Associated malignancy	Gonzalez	1989	10	2	20.00
Arthritis	Stuart	1989	14	1	7.14
Arthritis (Rheumatoid)	Salvarani	1999	30	6	20.00
Cranial manifestations (headaches, scalp tenderness, jaw claudication, ophthalmologic symptoms)	de Boysson	2016	143	112	78.32
Central retinal artery occlusion	Garrity	2017	116	16	13.79
Cancer	Unizony	2017	6414	810	12.63
Cancer	Pugnet	2015	103	10	9.71
Chronic kidney disease	Unizony	2017	6414	583	9.09
Chronic obstructive pulmonary disease	Unizony	2017	6414	498	7.76
Claudication on mastication, deglutition	Kobayashi	2003	65	2	3.08
Claudication (masseter)	Fainaru	1979	47	10	21.28
Claudication (mandibular and/or lingual)	Rivero-Puente	2001	57	14	24.56
Dental abscess	Russo	1995	100	3	3.00
Deafness	Khalifa	2009	96	1	1.04
Dizziness	Haugeberg	2000	53	2	3.77
Dysphagia	Gonzalez-Gay	2005	240	12	5.00
Dysphagia	Kobayashi	2003	66	1	1.52
Dyspnoea	Desmet	1990	34	6	17.65
Dyslipidaemia	de Boysson	2016	143	37	25.87
Ear/nose/throat symptoms	Desmet	1990	34	11	32.35
Eye pain	Garrity	2017	116	16	13.79
Extracranial vessel involvement	Silva de Souza	2013	45	8	17.78
Extracranial manifestations	de Boysson	2016	143	68	47.55
Facial pain	Machado	1988	94	13	13.83
Facial pain	Alba	2011	11	5	45.45
Fracture or trauma	Unizony	2017	6414	126	1.96
Herpes Zoster (uncomplicated)	England	2017	5942	177	2.98

Clinical feature	Author(s)	Year	Total number of GCA cases	Clinical feature present (N)	Clinical feature present (%)
Herpes Zoster (complicated)	England	2017	5942	59	0.99
Hypercholesterolemia	Espitia	2012	22	5	22.73
Hypertension - systolic (>160 mm/Hg)	Kobayashi	2003	60	8	13.33
Inflammatory bowel disease	Unizony	2017	6414	81	1.26
Ischemic complications (Severe permanent cranial)	Alba	2011	11	3	27.27
Ischemic manifestations -severe	Sun	2016	70	29	41.43
Ischemic optic neuropathy - posterior	Garrity	2017	116	8	6.90
Ischemic stroke	Zenone	2013	88	5	5.68
Ischaemic attacks - transient	Sun	2016	70	1	1.43
Ischaemic stroke	Gonzalez-Lopez	2013	81	1	1.23
Infection - synovitis	Gabriel	1995	172	10	5.81
Infection - endocarditis	Kobayashi	2003	55	1	1.82
Infection - any	Russo	1995	100	63	63.00
Infection - amebiasis	Russo	1995	100	1	1.00
Infection - bacterial endocarditis	Russo	1995	100	1	1.00
Infection - bronchitis	Russo	1995	100	1	1.00
Infection - cellulitis	Russo	1995	100	1	1.00
Infection - diverticulitis	Russo	1995	100	1	1.00
Infection - otitis media	Russo	1995	100	1	1.00
Infection - upper respiratory tract	Russo	1995	100	4	4.00
Infection - pneumonia	Russo	1995	100	4	4.00
Infection - viral illness	Russo	1995	100	4	4.00
Infection - pharyngitis	Russo	1995	100	7	7.00
Infection - sinusitis	Russo	1995	100	8	8.00
Infection - urinary tract	Russo	1995	100	23	23.00
Loss of hearing	Fainaru	1979	47	8	17.02
Loss of appetite	Myklebust	1996	39	5	12.82
Lower limb arterial thrombosis	Khalifa	2009	96	1	1.04
Lung diseases	Pugnet	2015	103	1	0.97
Muscle atrophy	Kobayashi	2003	57	1	1.75
Night sweats	Myklebust	1996	39	10	25.64
Night sweats	Haugeberg	2000	53	4	7.55
Neck pain	Garrity	2017	101	20	19.80
Neck pain	Heyreh	1997	106	17	16.04
Oedema (facial/swelling)	Duhaut	1999	207	9	4.35

Clinical feature	Author(s)	Year	Total number of GCA cases	Clinical feature present (N)	Clinical feature present (%)
Oedema	Kobayashi	2003	57	1	1.75
Optic nerve atrophy	Kobayashi	2003	66	5	7.58
Pain in temporal artery region	Kobayashi	2003	65	38	58.46
Pain and stiffness in neck and shoulders	Gonzalez-Lopez	2013	81	42	51.85
Peripheral artery disease	Unizony	2017	6414	317	4.94
Pulmonary symptoms	Desmet	1990	34	12	35.29
Respiratory symptoms	Machado	1988	94	22	23.40
Skeletal and muscle manifestation	Kobayashi	2003	66	13	19.70
Submandibular glands	Russo	1995	100	2	2.00
Systematic arteritis	Gonzalez	1989	10	2	20.00
Taste changes	Myklebust	1996	39	4	10.26
Temporal tenderness (on exam)	Singh	2015	204	52	25.49
Temporal tenderness	Mohamed	2002	17	11	64.71
Temporal artery tenderness	Roth	1984	18	1	5.56
Temporal artery prominence	Gonzalez	1989	10	5	50.00
Temporal cutaneous hyperalgesia	Gonzalez-Lopez	2013	81	40	49.38
Varicose vein	Unizony	2017	6414	715	11.15
Vascular bruits	de Boysson	2016	143	14	9.79

3.5.5 Meta-analysis

There were 30 clinical features across 43 articles that were eligible for meta-analysis, 35 for prevalence, and 18 for association. The overall pooled prevalence estimates were determined from 30 individual meta-analyses, each examining the prevalence of a clinical feature experienced prior to GCA diagnosis. Prevalence of symptoms, signs, and laboratory tests reported prior to a diagnosis of GCA are reported here separately from comorbidities and are summarised in forest plots found in Appendix 3.4, Figures 1 – 29. Findings from the meta-analyses are presented in detail below, and summarised in Table 3.4 for the prevalence of all clinical features, and Table 3.5 for the associations.

The clinical features with the largest prevalence were headache, elevated ESR, and constitutional/systemic symptoms. Clinical features with the lowest prevalence were cerebrovascular accidents, psychological conditions, and limb claudication. Clinical features with the strongest association with GCA confirmed through a positive temporal artery biopsy were jaw claudication, elevated ESR, and anorexia. Clinical features with the weakest associations were fever, PMR, and any visual symptoms.

Subgroup analysis for prevalence, stratified by point at which clinical features were reported, was conducted for 13 clinical features (Appendix 3.5, Table 1). The largest subgroup was at diagnosis/TAB, where the clinical features were recorded at or prior to the patient's diagnosis of GCA. Meta-regression were conducted only on clinical features with sufficient articles for prevalence (Appendix 3.6, Table 1). No estimate of association for any clinical feature was reported in enough articles to conduct a meta-regression. The association (odds ratio) between clinical features and a subsequent diagnosis of GCA are summarised in Table 3.5, and forest plots can be seen in Appendix 3.7, Figures 1 – 12.

Table 3.4: Pooled prevalence estimates of reported clinical features.

Clinical feature	N	Pooled prevalence (%)	95% CI	95% PI	I^2 (%)	τ^2
Headache	35	77	(72%, 82%)	(47%, 97%)	89.2	0.02
Elevated ESR (>50 mm/h)	8	76	(59%, 90%)	(25%, 100%)	94.5	0.06
Constitutional/systemic symptoms	15	62	(48%, 74%)	(14%, 98%)	96.4	0.06
Abnormal temporal artery	30	54	(42%, 65%)	(9%, 95%)	95.8	0.06
Fatigue	7	45	(32%, 57%)	(15%, 77%)	89.2	0.02
Any visual impairment	31	44	(34%, 53%	(3%, 90%)	95.8	0.07
Anorexia	9	37	(25%, 50%)	(6%, 76%)	91.6	0.03
Jaw Claudication	32	36	(31%, 41%)	(14%, 61%)	84.9	0.02
Neurological conditions	5	35	(9%, 67%)	(0%, 98%)	95.9	0.12
PMR	32	34	(29%, 39%)	(12%, 61%)	86.7	0.02
Malaise	6	34	(20%, 50%)	(5%, 72%)	90.7	0.03
Scalp tenderness	17	34	(26%, 42%)	(9%, 65%)	90.6	0.02
Weight loss	17	34	(28%, 41%)	(13%, 60%)	83.5	0.02
Ischaemic optic neuropathy	6	32	(11%, 58%)	(0%, 92%)	96.3	0.10
Arthralgia	3	31	(21%, 43%)	(21%, 43%)	0.0	0.00
Hypertension	3	31	(10%, 58%)	(0%, 82%)	97.8	0.06
Fever	26	30	(23%, 37%)	(4%, 65%)	91.3	0.03
Smoking	4	28	(11%, 48%)	(1%, 71%)	94.7	0.04
Cardiovascular diseases	3	28	(4%, 61%)	(0%, 88%)	96.5	0.08
Myalgia	5	26	(11%, 43%)	(0%, 66%)	88.2	0.03
Peripheral arthritis	3	19	(0%, 56%)	(0%, 88%)	96.3	0.11
Ophthalmic symptoms	3	19	(10%, 30%)	(5%, 39%)	68.9	0.08
Ocular symptoms	4	18	(7%, 33%)	(0%, 51%)	83.2	0.02
Anaemia	3	18	(10%, 27%)	(7%, 32%)	49.9	0.04
Amaurosis Fugax	5	16	(6%, 30%)	(0%, 50%)	84.6	0.03
Cough	4	13	(3%, 28%)	(0%, 49%)	91.1	0.03
Diabetes	4	13	(4%, 24%)	(0%, 40%)	93.2	0.02
Diplopia	8	6	(5%, 8%)	(5%, 8%)	0.0	0.00
Cerebrovascular accidents	6	7	(2%, 13%)	(0%, 26%)	92.7	0.02
Psychological conditions	4	5	(1%, 12%)	(0%, 19%)	72.4	0.01
Limb claudication	4	3	(1%, 4%)	(1%, 4%)	0.0	0.00

Table 3.5: Pooled associations of symptoms with GCA diagnosis.

Clinical feature	**N**	**Pooled Odds Ratios**	**95% CI**	**95% PI**	**I^2 (%)**	**τ^2**
Jaw claudication	13	**4.84**	(3.55, 6.58)	(2.50, 9.37)	32.0	0.09
Elevated ESR	7	**2.22**	(1.71, 2.87)	(1.47, 3.34)	21.7	0.03
Anorexia	4	**2.00**	(1.41, 2.83)	(1.41, 2.83)	0.0	0.00
Constitutional symptoms	6	1.94	(0.96, 3.92)	(0.41, 9.26)	75.8	0.51
Headache	14	**1.75**	(1.16, 2.62)	(0.50, 6.06)	72.4	0.04
Scalp tenderness	4	1.63	(0.99, 2.66)	(0.99, 2.66)	0.0	0.00
Abnormal Temporal artery	8	1.43	(0.58, 3.55)	(0.12, 17.44)	90.2	1.41
Malaise	3	1.34	(0.87, 2.05)	(0.87, 2.05)	0.0	0.00
Myalgia	4	1.27	(0.83, 1.96)	(0.83, 1.96)	0.0	0.00
Fever	7	1.25	(0.92, 1.72)	(0.79. 1.99)	16.6	0.03
PMR	11	1.07	(0.84, 1.36)	(0.84, 1.36)	0.0	0.00
Any visual symptoms	14	0.97	(0.63, 1.48)	(0.26, 3.58)	71.6	0.40
Ocular symptoms	3	0.74	(0.45, 1.20)	(0.45, 1.20)	0.0	0.00

Results in bold indicate statistical significance.

3.5.5.1 Headache

Headache was assessed in 35 articles included in this study (Table 3.4), and was the most reported clinical feature in this systematic review. It had the highest overall pooled prevalence of 77% (95% CI: 77%, 82%; 95% PI: 47%, 97%). Heterogeneity was high with an I^2 of 89.2% ($\tau^2 = 0.02$).

The meta-analysis on the prevalence of headache (Figure 3.2) contained four subgroups, based on the point at which headache was recorded prior to a diagnosis of GCA, these included; at diagnosis/TAB (n = 29), at referral to secondary care (n = 3), at disease onset (n = 2), and average 35 days prior (n = 1). The pooled prevalence for at diagnosis/TAB was 78% (95% CI: 72%, 83%), which is similar to the overall estimate for all subgroups (77%). All remaining subgroups (at referral, at disease onset and 35 days prior groups) were too small to conduct a subgroup analysis, containing two, two, and one article, respectively.

The heterogeneity for headache prevalence was high so a meta-regression was conducted. The covariate that explained most of the heterogeneity between studies was year of publication. In papers published between 2001 and 2010 the prevalence for headache was 15.8% higher than for papers published between 1970 and 2000. This was a statistically significant result. Whereas papers published between 2011 and present had a non-statistically significant decrease in prevalence of 5.6% compared to papers published in 1970-2000. Categorised year of publication explained 37.6% of the heterogeneity.

The other statistically significant result for this analysis was continent of origin. Articles from Europe had a 12.6% increase in prevalence of headache than those conducted in the Americas. The multivariable model, fitted with year of publication and continent of origin, showed a statistically significant increase in the prevalence of headache in articles published from 2001-2010.

Fourteen articles reported an odds ratio estimate of the association between headache and subsequent GCA (Table 3.5 & Figure 3.3). The pooled OR was 1.75 (95% CI: 1.16, 2.62; 95% PI: 0.50, 6.06) indicating that patients reporting a headache had 1.75 times higher odds of a subsequent GCA diagnosis. Heterogeneity was high with an I^2 of 72.4% ($\tau^2 = 0.04$). Thirteen articles that reported an odds ratio recorded a headache at the time of diagnosis/temporal artery biopsy. The remaining article (Hayreh et al., 1997) recorded headache at the time of referral.

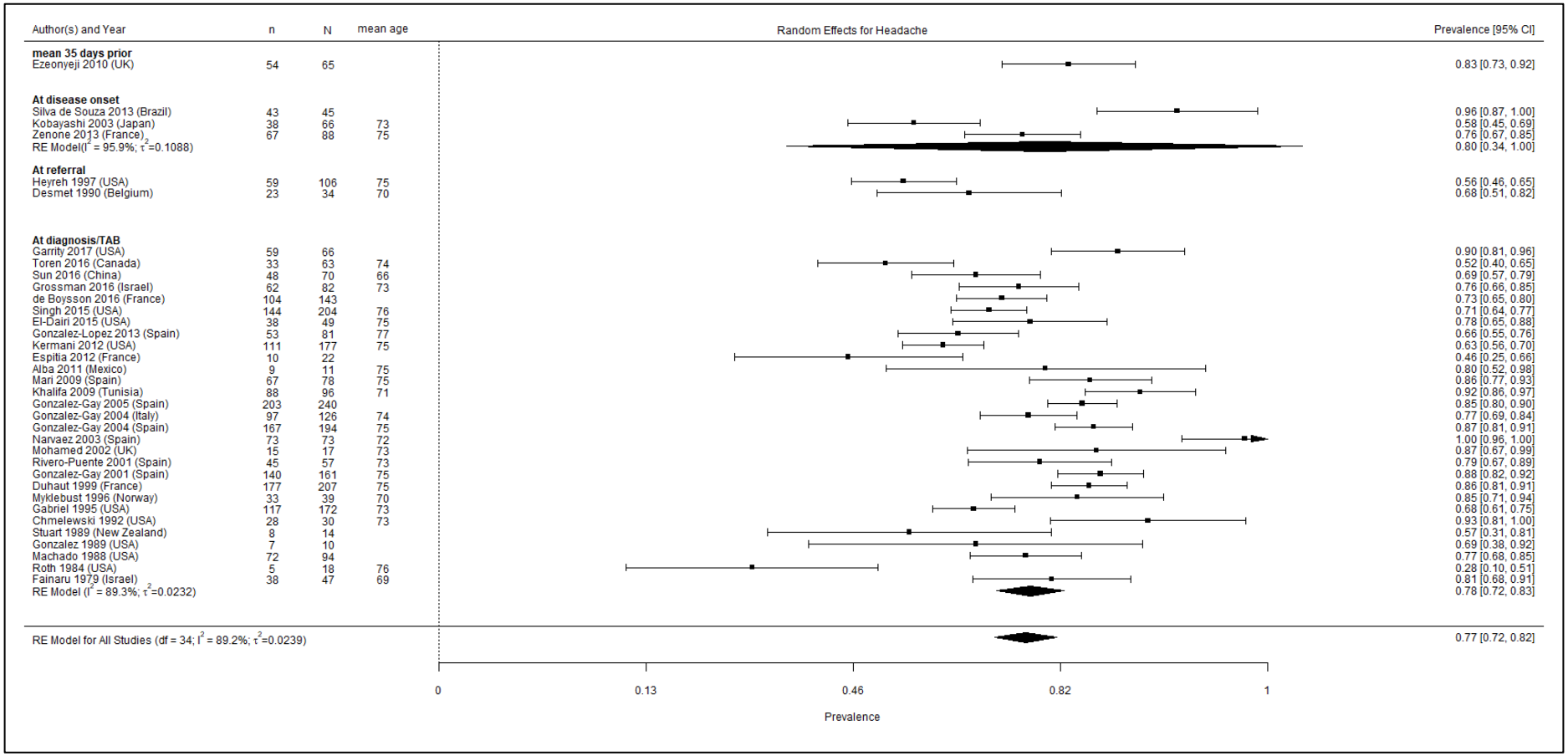


Figure 3.2: Forest plot for prevalence of Headache meta-analysis showing number of GCA cases in study (n), total sample size (N), mean age of study population (mean age), country of origin, prevalence estimates, and 95% confidence intervals.

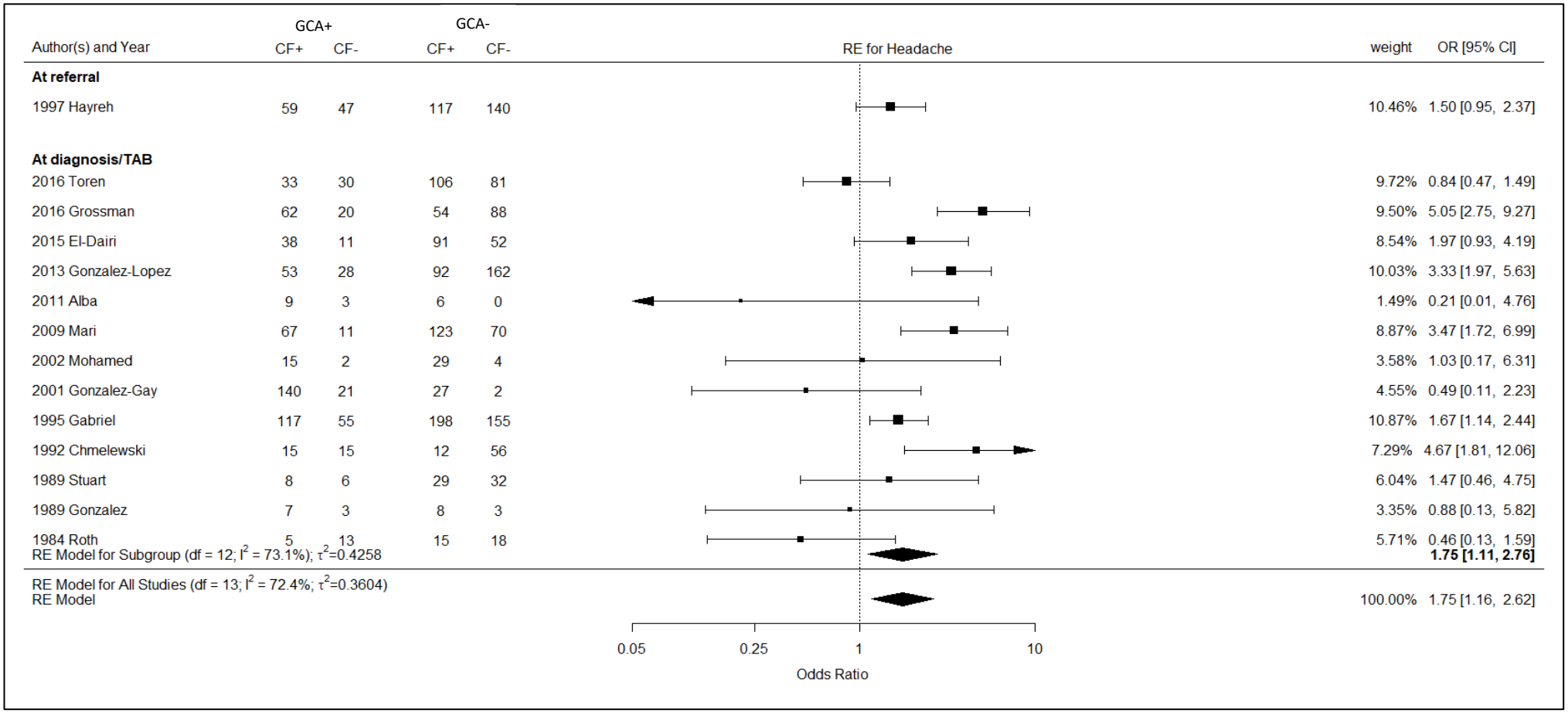


Figure 3.3: Forest plot of meta-analysis of association of headache and a diagnosis of GCA. Showing; diagnosis status (GCA+, GCA-), clinical feature present (CF+, CF-), weights and reported ORs for each study with 95% CIs, and the overall pooled OR.

3.5.5.2 Elevated ESR

Elevated ESR was assessed in eight of the articles included in this review, with an overall pooled prevalence of 76% (95% CI: 59%, 90%; 25%, 100%). Heterogeneity was high with an I^2 of 94.5% (τ^2 = 0.06). A forest plot can be seen in Appendix 3.5, Figure 1.

Elevated ESR was recorded at diagnosis/TAB in all included articles. There were three articles where the prevalence estimate differed considerably from the overall pooled result found in the meta-analysis. An older study, Machado et al (1988), found the prevalence of elevated ESR amongst GCA patients was 97%. Chmelewski (1992) and Toren (2016) reported the prevalence of elevated ESR in their study populations as 40% and 49%, respectively. Due to there being fewer than 10 articles reporting elevated ESR, a meta-regression could not be conducted.

An odds ratio was reported in seven articles, with a pooled odds ratio of 2.22 (95% CI: 1.71, 2.87); 95% PI: 1.47, 3.34) suggesting a strong association between elevated ESR and GCA. Patients with elevated ESR have more than 2 times higher odds of a subsequent GCA diagnosis. Heterogeneity for this meta-analysis was low, with an I^2 of 21.7 (τ^2 = 0.03). All seven articles recorded elevated ESR at the time of diagnosis/temporal artery biopsy. A forest plot can be seen in Appendix 3.7, Figure 1.

3.5.5.3 Constitutional/Systemic symptoms

Constitutional/systemic symptoms were reported in 15 articles, with an overall pooled prevalence of 62% (95% CI: 48%, 74%; 95% PI: 14%, 98%). Heterogeneity was high, with an I^2 of 96.4% (τ^2 = 0.06) (Appendix 3.5, Figure 2). The majority of articles (80%) recorded constitutional/systemic symptoms at diagnosis/TAB. The pooled prevalence estimate for this subgroup was 62% (95% CI: 48%, 75%). One article recorded these symptoms at referral

(Desmet et al., 1990), one at disease onset (Silva de Souza et al., 2013), and the final study on average 35 days prior to a diagnosis of GCA (Ezeonyeji et al., 2011b).

There were enough articles to conduct a meta-regression. The three variables that explained most of the heterogeneity in prevalence were continent, proportion of females, and year of publication. Prevalence of constitutional/systemic symptoms was 48.1% higher in Europe than America, and 46.5% higher in other parts of the world than America, these were statistically significant results. The prevalence of constitutional/systemic symptoms was 44.9% lower in articles published from 2011-present than those published between 1970 and 2000, again this was statistically significant. As the proportion of females in the study sample increased by 1%, the prevalence of constitutional/systemic symptoms increased significantly by 1.2%.

The multivariable model with continent, year of publication, and proportion of females explained 96.5% of the total heterogeneity. Articles published between 2001 and 2011 had an adjusted 31.7% lower prevalence of constitutional/systemic symptoms, and articles published between 2011 and present had 46.0% lower prevalence than articles published between 1970 and 2000, which were statistically significant. Proportions of females in the study sample was the only non-significant variable. The prevalence of constitutional/systemic symptoms was an adjusted 60.1% higher in Europe, and 69.1% higher in other countries than in America. These were statistically significant.

An odds ratio of constitutional/systemic symptoms was reported in six articles. The overall pooled odds ratio was 1.94 (95% CI: 0.96, 3.92; 95% PI: 0.41, 9.26), indicating an association, which is not statistically significant, between constitutional/systemic symptoms and GCA. Heterogeneity was high, with an I^2 of 75.8% ($\tau^2 = 0.51$). Five articles recorded constitutional/systemic symptoms at the time of diagnosis/temporal artery biopsy. The

remaining article (Hayreh et al., 1997) recorded constitutional/systemic symptoms at the time of referral. A forest plot can be seen in Appendix 3.7, Figure 2.

3.5.5.4 Abnormal Temporal Artery

Abnormal temporal artery (defined as tenderness, swelling, prominence, or pulsating) was recorded in twenty articles. The overall pooled prevalence was 54% (95% CI: 42%, 65%; 95% PI: 9%, 95%). Heterogeneity was high, with an I^2 of 95.8% ($\tau^2 = 0.06$). A forest plot can be seen in Appendix 3.5, Figure 3.

There were two subgroups of time of feature recording. Three articles recorded features at referral (Desmet et al., 1990; Hayreh et al., 1997; Zenone & Puget, 2013), whilst the remaining articles recorded features at diagnosis/TAB. The pooled prevalence of the "at referral" subgroup was 27% (95% CI: 17%, 39%), and 58% (95% CI: 46%, 70%) for the at diagnosis/TAB subgroup.

There were sufficient articles in the "at diagnosis/TAB" subgroup to conduct a meta-regression to investigate the high heterogeneity. The covariate that explained the most heterogeneity in the univariable model was year of publication. Articles published between 2001 and 2010 had 29.2% higher prevalence of abnormal temporal artery than those published between 1970 and 2000. This was statistically significant. Overall year of publication explained 46.2% of the total heterogeneity. When added to a multivariable model, along with continent, studies published between 2001 and 2010 had an adjusted 21.9% higher prevalence of abnormal temporal artery than those published between 1970 and 2000. However, year of publication was no longer statistically significant. The multivariable model with continent and year of publication explained 41.7% of the heterogeneity.

An odds ratio was reported in eight of the articles relating to the presence of an abnormal temporal artery prior to GCA diagnosis. The overall pooled OR was 1.43 (95% CI: 0.58, 3.55; 95% PI: 0.12, 17.44) suggesting an association between abnormal temporal artery and a GCA diagnosis. Patients with an abnormal temporal artery have 1.43 times higher odds of a GCA diagnosis. Heterogeneity was high with an I^2 of 90.2% (τ^2 = 1.41). Seven of the articles recorded abnormal temporal artery at diagnosis/temporal artery biopsy. The remaining article (Hayreh et al., 1997) recorded abnormal temporal artery at the time of referral. A forest plot can be seen in Appendix 3.7, Figure 3.

3.5.5.5 Fatigue

Fatigue was reported in seven articles included in the review. The overall pooled prevalence was 45% (95% CI: 32%, 57%; 95% PI: 15%, 77%). Heterogeneity was high with an I^2 of 89.2% (τ^2 = 0.02). A forest plot can be seen in Appendix 3.5, Figure 4.

All but one article reported fatigue at diagnosis/TAB (Desmet et al., 1990). The article by Desmet et al (1990) reported fatigue at referral to secondary care. It did not state the length of time between being referred and being diagnosed with GCA. This article was conducted in Belgium and rated as being of good quality on the Newcastle-Ottowa scale. They confirmed GCA diagnosis by temporal artery biopsy and found a total of 34 GCA cases. The prevalence of fatigue in this sample of patients was reported to be 79%, higher than the overall pooled estimate of 45%. No articles included in the review reported the association of fatigue with GCA diagnosis.

3.5.5.6 Visual impairment

Visual impairment was reported in thirty-one articles. Visual impairment included any type of visual condition, such as blindness and blurred vision. The overall pooled prevalence was 44% (95% CI: 34%, 53%; 95% PI: 3%, 90%). Heterogeneity was high with an I^2 of 95.8% (τ^2 = 0.07). A forest plot can be seen in Appendix 3.5, Figure 5.

In the univariable model of the meta-regression, year of publication explained most of the heterogeneity (37.6%). Articles published between 2001 and 2010 had 15.8% higher prevalence of visual impairment than articles published between 1970 and 2000, this was a statistically significant result. However, when added to a multivariable model with continent and study quality, this model only explained 27.1% of the heterogeneity.

An odds ratio for visual impairment was reported in fourteen articles. The overall pooled odds ratio was 0.97 (95% CI: 0.63, 1.48; 95% PI: 0.26, 3.58) indicating no association with GCA diagnosis. Heterogeneity was high with an I^2 of 71.6% (τ^2 = 0.07). All fourteen articles recorded visual impairment at the time of diagnosis/temporal artery biopsy. A forest plot can be seen in Appendix 3.7, Figure 4.

3.5.5.7 Anorexia

Anorexia (interpreted as loss of appetite in this systematic review) was reported in nine articles. The overall pooled prevalence was 37% (95% CI: 25%, 50%; 95% PI: 6%, 76%). Heterogeneity was high with an I^2 of 91.6% (τ^2 = 0.03). A forest plot can be seen in Appendix 3.5, Figure 5.

There were two articles that differed considerably from the pooled estimate. Desmet et al (1990) reported the prevalence of anorexia in their study as 74%. This was a single-centre

cohort study conducted in Belgium that was rated good on the Newcastle-Ottowa scale and recruited 34 patients with a positive temporal artery biopsy.

The second outlier was a cohort study conducted in the USA (T.A. Kermani et al., 2012). The article reviewed the records of patients who had undergone a temporal artery biopsy using the Mayo clinic database. Of the 177 patients who had a positive temporal artery biopsy the prevalence of anorexia in this population was reported to be 11%.

An odds ratio for anorexia was reported in four articles. The overall pooled odds ratio was 2.00 (95% CI: 1.41, 2.83; 95% PI: 1.41, 2.83) indicating that patients with anorexia have two times higher odds of a GCA diagnosis. Heterogeneity was low, with an I^2 of 0.0% ($\tau^2 = 0.00$). A forest plot can be seen in Appendix 3.7, Figure 5. Three articles recorded anorexia at diagnosis/temporal artery biopsy, whilst the remaining article (Hayreh et al., 1997) recorded it at the time of referral.

3.5.5.8 Jaw claudication

Thirty-two articles reported jaw claudication. The overall pooled prevalence was 36% (95% CI: 31%, 41%; 95% PI: 14%, 61%). Heterogeneity was high with an I^2 of 84.9% ($\tau^2 = 0.02$). A forest plot can be seen in (Figure 3.4).

The majority of articles recorded jaw claudication at diagnosis/TAB (26 studies), enough to conduct a meta-regression. The univariable model that explained most of the heterogeneity (37.5%) was type of diagnosis. Patients diagnosed using the ACR criteria had 6.4% higher prevalence of jaw claudication than those diagnosed using TAB; however, this was not statistically significant. The only statistically significant relationship was the 29.5% lower prevalence of jaw claudication in those diagnosed by other means compared to a TAB. Type of diagnosis was added to a multivariable model with mean age, which explained 14.2% of

the heterogeneity in the univariable model. The multivariable model explained 72.7% of the heterogeneity. Only the association between other methods of diagnosis and the prevalence of jaw claudication was statistically significant. Those diagnosed with other means had an adjusted 27.9% lower prevalence of jaw claudication than those diagnosed using TAB.

Thirteen articles recorded an odds ratio of jaw claudication. The overall pooled OR was 4.84 (95% CI: 3.55, 6.58; 95% PI: 2.50, 9.37), the largest pooled odds ratio found in the association meta-analysis. Heterogeneity was low/moderate with an I^2 of 32.0% ($\tau^2 = 0.09$). A forest plot can be seen in Appendix 3.7, Figure 6. Twelve articles recorded jaw claudication at the time of diagnosis/temporal artery biopsy. The remaining article (Hayreh et al., 1997) recorded it at the time of referral.

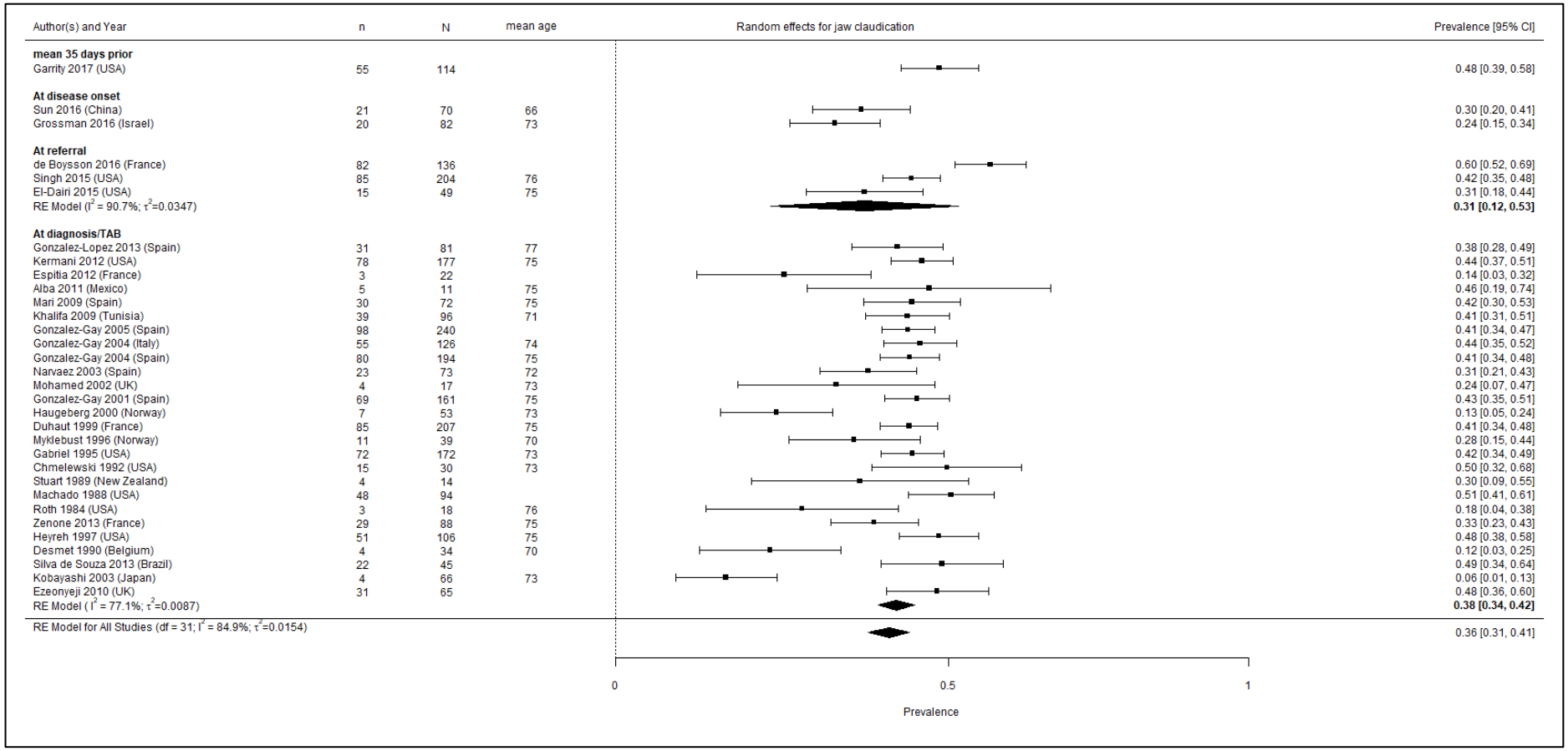


Figure 3.4: Forest plot for prevalence of jaw claudication meta-analysis showing number of GCA cases in study (n), total sample size (N), mean age of study population (mean age), country of origin, prevalence estimates, and 95% confidence intervals.

3.5.5.9 Neurological conditions

Four articles included in the review reported neurological conditions. The overall pooled prevalence was 35% (95% CI: 9%, 67%; 95% PI: 0%, 98%). Heterogeneity was high, with an I^2 of 95.9% ($\tau^2 = 0.12$). A forest plot can be seen in Appendix 3.5, Figure 8.

Three of the five articles (Chmelewski et al., 1992; Khalifa et al., 2009; Mohamed & Bates, 2002) recorded neurological conditions at the time of diagnosis/TAB, whilst the remaining 2 (Kobayashi et al., 2003; Souza et al., 2013) recorded them at disease onset.

Kobayashi et al (2003), a cohort study conducted in Japan, reported the prevalence of neurological conditions in their population of 66 confirmed GCA cases as 78%. This article did not define what neurological conditions were included. No articles assessed the association between neurological conditions and a diagnosis of GCA.

3.5.5.10 PMR

Thirty-two studies reported on PMR prior to GCA diagnosis. The pooled prevalence of PMR was 34% (95% CI: 29%, 39%; 95% PI: 12%, 61%). Heterogeneity was high, with an I^2 of 86.7% ($\tau^2 = 0.02$). A forest plot can be seen in Appendix 3.5, Figure 9.

Twenty-seven articles reported PMR at diagnosis/TAB. One (C. Salvarani & Hunder, 1999) recorded clinical features a median of 30 months prior to a diagnosis of GCA. One (Desmet et al., 1990) recorded PMR at the time of referral to secondary care, without stating how long before diagnosis this period was. Two (Kobayashi et al., 2003; Silva de Souza et al., 2013) recorded PMR at the time of disease onset, but did not define how long this was prior to a diagnosis of GCA. One (Ezeonyeji, Borg, & Dasgupta, 2011a) recorded clinical features with a reported average of 35 days prior to a diagnosis of GCA.

There was high heterogeneity in the prevalence meta-analysis and enough articles to conduct a meta-regression. In the univariable models, the covariate that explained the largest amount of heterogeneity was year of publication (19.4%); however, only one level of this variable was statistically significant. Articles published between 2011 and 2017 had 14.9% lower prevalence of PMR than those published prior to 2000. There were two other covariates in the model that explained a proportion of the heterogeneity; continent (12.3%), and proportion of females (1.6% per 1% increase in proportion of females). This model explained 54.0% of the heterogeneity. Statistically significant results showed that articles published in other continents had an adjusted 22.8% higher prevalence of PMR than those published in the Americas, the prevalence of PMR increased by 0.5% with every increase in 1% of population who were female, and articles published from 2011-2017 had 16.9% lower adjusted prevalence of PMR than those published prior to 2000.

Eleven articles reported an odds ratio for PMR. The overall pooled OR was 1.07 (95% CI: 0.84, 1.36; 95% PI: 0.84, 1.36) suggesting no association of PMR with GCA. Heterogeneity was low, with an I^2 of 0.0% ($\tau^2 = 0.00$). A forest plot can be seen in Appendix 3.7, Figure 7. All articles recorded PMR at the time of diagnosis/temporal artery biopsy.

3.5.5.11 Malaise

Six articles included in this review reported their findings on malaise (general discomfort, weakness, or not feeling well). The overall pooled prevalence was 34% (95% CI: 20%, 50%; 95% PI: 5%, 72%). Heterogeneity was high, with an I^2 of 90.7% ($\tau^2 = 0.03$). A forest plot can be seen in Appendix 3.5, Figure 10.

Five articles recorded malaise at the time of diagnosis/TAB, whilst the remaining one (Hayreh et al., 1997) recorded it at the time of referral to secondary care, without defining

how long this period was. All but two articles (Duhaut, Pinède, et al., 1999; Dunstan et al., 2014) showed a prevalence of malaise between 30% and 40%. Dunstan et al (2014) conducted a cohort study in South Australia that was rated as fair on the Newcastle-Ottowa scale. The method of GCA diagnosis used in the study was a temporal artery biopsy, and malaise was recorded at the time of diagnosis/TAB. The article found 314 biopsy-proven cases of GCA, 59% of which recorded malaise as a symptom prior to their diagnosis of GCA. Duhaut et al (1999) conducted a cohort study in France, which was rated as fair on the Newcastle-Ottowa scale. They identified GCA patients using a combination of a variation of the ACR criteria and a positive temporal artery biopsy and recorded clinical features at the time of diagnosis/TAB. This article included information on 207 biopsy-proven GCA cases, 72.9% were female and the mean age was 74.9 years. The reported prevalence of malaise in this study population was 11%, lower than the overall pooled prevalence of 34%.

Three articles reported an odds ratio for malaise. The overall pooled OR was 1.34 (95% CI: 0.87, 2.05; 95% PI: 0.87, 2.05) indicating a (non-statistically significant) association between malaise and a GCA diagnosis. Heterogeneity was low, with an I^2 of 0.0% ($\tau^2 = 0.00$). A forest plot can be seen in Appendix 3.7, Figure 8. Two articles recorded malaise at the time of diagnosis/temporal artery biopsy, whilst the remaining article recorded it at the time of referral (Hayreh et al., 1997).

3.5.5.12 Scalp tenderness

Seventeen articles included scalp tenderness as a clinical feature for assessment. The overall pooled prevalence of scalp tenderness was 34% (95% CI: 26%, 42%; 95% PI: 9%, 65%) and heterogeneity was high, with an I^2 of 90.6% ($\tau^2 = 0.02$). A forest plot can be seen in Appendix 3.5, Figure 11.

All but three articles recorded this symptom at diagnosis/TAB. One (Hayreh et al., 1997) recorded it at referral to secondary care. One (Kobayashi et al., 2003) recorded it at disease onset. The remaining article (Ezeonyeji et al., 2011a) recorded clinical features with a mean of 35 days prior to the date of GCA diagnosis.

A meta-regression model was fitted to the data. The univariable model that explained the largest amount of heterogeneity was type of diagnosis (51.0%). The only statistically significant result showed that studies which used other methods of diagnosing GCA had 42% lower prevalence of scalp tenderness than articles that used a temporal artery biopsy. The other univariable model that explained the most heterogeneity was study quality, and these variables were all added into the multivariable model. This model explained 70.6% of the heterogeneity. The statistically significant results showed that articles of fair quality had 17.8% lower adjusted prevalence of scalp tenderness than those of good quality, and articles that used other means of GCA diagnosis had 37% lower adjusted prevalence of scalp tenderness than those that used a temporal artery biopsy.

An odds ratio of scalp tenderness was reported in four articles. The overall pooled OR was 1.63 (95% CI: 0.99, 2.66; 95% PI: 0.99, 2.66). Heterogeneity was low, with an I^2 of 0.0% (τ^2 = 0.00). A forest plot can be seen in Appendix 3.7, Figure 9. Only one article did not record scalp tenderness at the time of diagnosis/temporal artery biopsy. Instead it recorded scalp tenderness at the time of referral (Hayreh et al., 1997).

3.5.5.13 Weight loss

Seventeen articles reported weight loss as a clinical feature. The overall pooled prevalence was 34% (95% CI: 28%, 41%; 95% PI: 13%, 60%). Heterogeneity was high, with an I^2 of 83.5% (τ^2 = 0.02). A forest plot can be seen in Appendix 3.5, Figure 12.

All but three of the articles recorded weight loss at the time of diagnosis/TAB. One article (Desmet et al., 1990) recorded this symptom at the time of referral to secondary care. Two articles (Kobayashi et al., 2003; Silva de Souza et al., 2013) recorded weight loss at disease onset.

There were enough articles that recorded weight loss at diagnosis/TAB to conduct a meta-regression. In the univariable model the covariate that explained the largest amount of heterogeneity was mean age (100.0%). With every year increase in mean age there was a 2.5% decrease in the prevalence of weight loss, this was a statistically significant result. Other variables that explained some of the heterogeneity in univariable models were proportion of females in the study sample (44.2%) and continent (33.9%). However, when these were added into the multivariable model they did not explain as much of the heterogeneity as the univariable model containing mean age. No articles reported the association between weight loss and GCA.

3.5.5.14 Ischaemic optic neuropathy

Ischaemic optic neuropathy (ION) was reported in six articles. The overall pooled prevalence was 32% (95% CI: 11%, 58%; 95% PI: 0%, 92%). Heterogeneity was high with an I^2 of 96.3% (τ^2 = 0.10). A forest plot can be seen in Appendix 3.5, Figure 13.

Half of the articles (Garrity et al., 2017; Gonzalez-Lopez et al., 2013; Roth, Milsow, & Keltner, 1984) recorded ischaemic optic neuropathy at the time of diagnosis/TAB. Two articles

(Kobayashi et al., 2003; Silva de Souza et al., 2013) recorded the symptom at disease onset. The final article (Zenone & Puget, 2013) recorded it at referral to secondary care.

Two articles (Garrity et al., 2017; Silva de Souza et al., 2013) had a higher reported prevalence than the overall pooled result at 69% and 76% respectively. Silva de Souza et al (2013) used the ACR criteria to identify patients with GCA, along with two other articles (Kobayashi et al., 2003; Zenone & Puget, 2013), which reported the prevalence as 16% and 15% respectively. None of the six articles were conducted in the same country. Garrity et al (2017) recorded ION at the time of diagnosis; however, two other articles (Gonzalez-Lopez et al., 2013; Roth et al., 1984) also recorded it at the same time and reported the prevalence as 12% and 15% respectively. There is no apparent explanation as to why Silva de Souza et al's (2013) article and Garrity et al's (2017) reported high prevalence of ION.

The study by Gonzalez-Lopez et al (2013) was the only case-control study to report ION. They found that patients with ION had 1.67 times higher odds of being diagnosed with GCA than controls who had no history of GCA. However, this relationship was not statistically significant (95% CI: 0.79, 3.50).

3.5.5.15 Arthralgia

Arthralgia (joint pain) was one of the least reported clinical features in this review, reported in three articles. The overall pooled prevalence in these three articles was 31% (95% CI: 21%, 43%; 95% PI: 21%, 43%). Heterogeneity was low, with an I^2 of 0.0% ($\tau^2 = 0.00$). A forest plot can be seen in Appendix 3.5, Figure 14.

All articles recorded arthralgia at the time of diagnosis/TAB. Two articles (Gonzalez, Varner, Lisse, Collins, & Daniels, 1986; Roth et al., 1984) were cohort studies conducted in the USA, and used a positive temporal artery biopsy to identify patients with GCA. The final article

(Fainaru et al., 1979) was a cohort study conducted in Israel and also used a positive temporal artery biopsy to identify GCA patients. This article was the only one to be rated as poor on the Newcastle-Ottowa scale, whilst the remaining two (Gonzalez et al., 1986; Roth et al., 1984) were rated as good. Article sample sizes varied from 10 to 47, whilst the prevalence estimates ranged from 22% to 50%. Gonzalez et al (1986) had the smallest sample size and reported the largest prevalence of 50%.

3.5.5.16 Hypertension

Three articles included in this review reported hypertension as a clinical feature. The overall pooled prevalence was 31% (95% CI: 10%, 58%; 95% PI: 0%, 82%). Heterogeneity was high, with an I^2 of 97.8% ($\tau^2 = 0.06$). A forest plot can be seen in Appendix 3.5, Figure 15. Prevalence varied across the three studies. Two were conducted in Europe, France and the UK (de Boysson et al., 2016; Unizony et al., 2017). Unizony et al (2017) used electronic health records (EHR) from the UK based health research network, THIN, whilst de Boysson et al (2016) used the medical records from three university hospitals in France. Unizony et al (2017) used medical Read codes and a record of a prescription for glucocorticoids to define GCA cases, whereas de Boysson et al (2016) used the ACR criteria. The reported prevalence of hypertension in their study samples was similar, with Unizony et al (2017) finding it recorded in 42% of their sample, whilst de Boysson et al (2016) recorded it in 46%. Kobayashi et al (2003) was an outlier to these and reported the prevalence of hypertension as 9%. This article had the smallest sample size, reporting their findings on 60 GCA cases identified using the ACR criteria. This difference in prevalence could be due to the overall prevalence of hypertension in the Asian population, reported to be less than the prevalence in other continents (Otani, Haruyama, & Gilmour, 2018).

3.5.5.17 Fever

Fever was reported in twenty-six articles included in this review. The overall pooled prevalence was 30% (95% CI: 23%, 37%; 95% PI: 4%, 65%). Heterogeneity was high, with an I^2 of 91.3% (τ^2 = 0.03). A forest plot can be seen in Appendix 3.5, Figure 16.

Two articles (Desmet et al., 1990; Hayreh et al., 1997) recorded fever at the time of referral to secondary care, whilst two articles (Kobayashi et al., 2003; Silva de Souza et al., 2013) recorded fever at disease onset. The remaining 22 articles reported fever at the time of diagnosis/TAB.

There was enough articles to conduct a meta-regression and in the univariable models, the covariate that explained the most heterogeneity was the mean age of the study sample (24.9%). With every year increase in the mean age there was a 3.6% statistically significant decrease in the prevalence of fever. Continent of origin explained 10.9% of the heterogeneity. If an article was conducted in "other" continents there was a 20.5% increase in the prevalence of fever compared with articles conducted in the Americas. As the proportion of females in the study sample increased by 1%, there was a 0.5% statistically significant decrease in the prevalence of fever. The final model included mean age and continent of origin, which explained 67.4% of the heterogeneity. The only statistically significant covariate was if an article was conducted in other continents they had 59.4% lower adjusted prevalence of fever than articles conducted in the Americas.

Seven articles reported the odds ratio of fever, six of which recorded fever at the time of diagnosis/TAB. The remaining article recorded fever at the time of referral (Hayreh et al., 1997). The overall pooled odds ratio was 1.25 (95% CI: 0.92, 1.72; 95% PI: 0.79. 1.99), indicating that patients who present with fever as a symptom have 25% higher odds of a positive temporal artery biopsy than those who do not. However, this was not a statistically

significant finding. Heterogeneity was low, with an I^2 of 16.6% (τ^2 = 0.03). A forest plot can be seen in Appendix 3.7, Figure 10.

3.5.5.18 Cardiovascular diseases

Three articles reported findings on cardiovascular diseases. The overall pooled prevalence was 28% (95% CI: 4%, 61%; 95% PI: 0%, 88%). There was a high level of heterogeneity between articles, with an I^2 of 88.2% (τ^2 = 0.08). A forest plot can be seen in Appendix 3.5, Figure 17.

Two articles (Espitia et al., 2012; A.G Singh et al., 2015) recorded cardiovascular diseases at the time of diagnosis/TAB, with the remaining article (Pugnet et al., 2015) recording clinical features that had occurred between 1 and 12 months prior to a diagnosis of GCA.

Espitia et al (2012) conducted secondary analysis of a cohort study in France that consecutively recruited 22 GCA patients over 18 months. To be diagnosed with GCA, patients had to have a positive temporal artery biopsy and satisfy 3 of the 5 ACR criteria. The article did not report the mean age of the sample or the gender distribution, and reported cardiovascular diseases in 63% of patients. Singh et al (2015) conducted a record review of all patients diagnosed with GCA between 1950 and 2004 in a single county, Minnesota, USA, by using the medical record linkage system available in the county. To be classed as having GCA, patients had to satisfy the ACR criteria. The mean age of the sample was 76 years, and 80% were female. Coronary artery disease was recorded at diagnosis in 20% of the GCA patients.

Pugnet et al (2015) conducted a case-control study in France using the French National Health Insurance system (FNHIS). GCA patients had to be 50 years of age or over, have an ICD-10 code for GCA in their record, and have at least one prescription of a glucocorticoid.

To be eligible as controls, patients could not have a history of GCA, PMR or vasculitis. Cases were matched with controls on a ratio of 1:6 on age, sex, and calendar year of diagnosis. Clinical features were reported if they had been in a patient's record between 1 and 12 months prior to their date of GCA diagnosis. This article did not define cardiovascular disease, and reported how many patients had "cardiovascular diseases" in their record. This article reported findings on 103 patients with GCA, with mean age of 75 years and 78% female. The prevalence of cardiovascular diseases in this sample was 11%.

Two of the articles (Espitia et al., 2012; Pugnet et al., 2015) were conducted in France, but reported vastly different prevalence estimates of cardiovascular diseases in patients with GCA. This could be due to a number of factors since country of origin was the only similarity between the two articles. They used different methods of classifying GCA patients (the ACR criteria and ICD-10 codes), and had differing, but small sample sizes (22 GCA patients and 103 GCA patients,). It is not possible to compare the study samples further as Espitia et al (2012) did not report sample characteristics in their article. Singh et al (2015) reported a similar estimate of cardiovascular disease to Pugnet et al (2015) (20% and 11%, respectively), and was the only article that reported cardiovascular diseases outside of Europe.

3.5.5.19 Myalgia

Myalgia was reported in five articles included in this review. The overall pooled prevalence was 26% (95% CI: 11%, 43%; 95% PI: 0%, 66%). Heterogeneity was high with an I^2 of 88.2% ($\tau^2 = 0.03$). A forest plot can be seen in Appendix 3.5, Figure 18.

All but one of the articles recorded clinical features at the time of diagnosis/temporal artery biopsy, with Hayreh et al (1997) recording myalgia at the time of referral to secondary care. Rivero-Puente et al (2001) conducted a cohort study in Spain. To be classified as having GCA,

patients had to have a positive temporal artery biopsy. A total of 57 patients were diagnosed with GCA, the mean age of the sample was 73 years, and 53% were female. The reported prevalence of myalgia in the study sample was 10%. Garrity et al (2017) conducted a cohort study in the USA and included data from 30 healthcare institutions. To be classified as having GCA, patients had to have a positive temporal artery biopsy. This article examined the differences in GCA between Caucasian patients and African-American patients, but for the purposes of this review these will be combined. The prevalence of myalgia in the combined study sample was 14%. Roth et al (1984) conducted a cohort study in the USA in a single secondary care centre. To be classified as having GCA, patients had to have a positive temporal artery biopsy. This article reported findings on 18 patients with GCA, recording clinical features at the time of diagnosis/temporal artery biopsy. The mean age of the sample was 76 years, with 71% female, and the prevalence of myalgia was 28%.

Hayreh et al (1997) conducted a cohort study in a single secondary care centre in the USA and patients with GCA were identified if they had a positive temporal artery biopsy. The mean age of the study sample was 72 years, with 66% being female and they reported the prevalence of myalgia in the 106 GCA patients as 29%. The largest prevalence estimate of myalgia was reported in Stuart et al's (1989) cohort study conducted in New Zealand. GCA patients were identified by a positive temporal artery biopsy. The mean age of the sample was not reported; however, 79% were female. This article reported the prevalence of myalgia as 64% in the 14 patients they identified as GCA positive.

The article conducted in Spain (Rivero Puente et al., 2001) reported the lowest prevalence of myalgia, whilst the articles conducted in the USA gave varying estimates from 14-29%. The largest prevalence was in New Zealand, at 64%. Despite only including 5 articles, heterogeneity between the articles was high, with an I^2 88.2%.

Four articles reported an odds ratio of myalgia. The overall pooled OR was 1.27 (95% CI: 0.83, 1.96; 95% PI: 0.83, 1.96). Heterogeneity was low, with an I^2 of 0.0% ($\tau^2 = 0.00$). A forest plot can be seen in Appendix 3.7, Figure 11.

3.5.5.20 Peripheral arthritis

Three articles included in this review reported findings on peripheral arthritis. The overall pooled prevalence was 19% (95% CI: 0%, 56%; 95% PI: 0%, 88%) and the heterogeneity of the meta-analysis was high, with an I^2 of 96.3% ($\tau^2 = 0.11$). A forest plot can be seen in Appendix 3.5, Figure 19.

The three articles recorded clinical features at different times prior to a diagnosis of GCA. Zenone et al (2013) conducted a cohort study in France, using the ACR criteria to identify patients with GCA at a single secondary care centre over a period of 11 years. The article reported clinical features of 88 patients with GCA at the time of their referral to secondary care. They reported the prevalence of peripheral arthritis in their study sample as 3%. Narvaez et al (2003) conducted a cohort study in Spain and used a combination of the ACR criteria and positive temporal artery biopsy to identify patients with GCA. Findings on clinical features were recorded at the time of diagnosis/temporal artery biopsy. They identified 73 patients with GCA, and the prevalence of peripheral arthritis in this sample was 11%. Salvarani et al (1999) conducted a cohort study in the USA, using a combination of the ACR criteria and positive temporal artery biopsies to identify patients with GCA. This article did not report the mean age or the gender distribution of the sample of 30 GCA patients. The prevalence of peripheral arthritis in this article was 57%.

3.5.5.21 Ophthalmologic symptoms

Three articles included in this review reported findings of ophthalmologic symptoms. The overall pooled prevalence is 19% (95% CI: 10%, 30%; 95% PI: 5%, 39%). Heterogeneity was moderate/high, with an I^2 of 69% ($\tau^2 = 0.08$). A forest plot can be seen in Appendix 3.5, Figure 20.

All three articles recorded ophthalmologic symptoms at different times prior to a diagnosis of GCA. Kobayashi et al (2003) conducted a cohort study in Japan, using the ACR criteria to identify patients with GCA, ophthalmologic symptoms were recorded at disease onset. The mean age of the sample was 73 years, and 64% were female. The reported prevalence of ophthalmologic symptoms was 11%. De Boysson et al (2016) conducted a cohort study in France, using the ACR criteria to identify GCA patients. Clinical features were recorded at the time of diagnosis/temporal artery biopsy. The reported prevalence of ophthalmologic symptoms was 21%. The final article, by Desmet et al (1990), was conducted in Belgium, and used the opinion of two medical professionals and a positive temporal artery biopsy to identify GCA patients. Clinical features were recorded at the time of referral to secondary care. The prevalence of ophthalmologic symptoms was 30%.

The two articles that used the ACR criteria (de Boysson et al., 2016; Kobayashi et al., 2003) had similar samples (mean age 73 years and 71 years, 64% and 66% of females, respectively) and reported low prevalence of ophthalmologic symptoms (11% and 21%, respectively). The country of origin was the main difference between these two articles. The two articles conducted in Europe (de Boysson et al., 2016; Desmet et al., 1990) had similar prevalence estimates of ophthalmologic symptoms (30% and 21%, respectively), but differing from Kobayashi et al (2003), which reported the smallest prevalence of 11%.

3.5.5.22 Ocular symptoms

Ocular symptoms were reported in four articles included in this review. The overall pooled prevalence of ocular symptoms was 18% (95% CI: 7%, 33%; 95% PI: 0%, 51%). Heterogeneity was high, with an I^2 of 83.2% (τ^2 = 0.02). A forest plot can be seen in Appendix 3.5, Figure 21. Three articles recorded ocular symptoms at the time of diagnosis/temporal artery biopsy (Chmelewski et al., 1992; Gabriel et al., 1995; Mohamed & Bates, 2002). Chmelewski et al (1992) conducted a cohort study in the USA and used a positive temporal artery biopsy to identify GCA patients. The reported prevalence of ocular symptoms in this study sample was 23%. Gabriel et al (1995) conducted a cohort study in the USA and used positive temporal artery biopsy to identify patients with GCA. The prevalence of ocular symptoms was 10%. Mohamed and Bates (2002) conducted a cohort study in the UK using positive temporal artery biopsy to identify patients with GCA in secondary care. The mean age of the sample was 71 years, with 71% female and a prevalence of ocular symptoms in this study population was 7%. The sample characteristics from these three articles is very similar, and two were conducted in the USA but have differing prevalence estimates of ocular symptoms. The remaining article by Kobayashi et al (2003) recorded ocular symptoms at the time of disease onset, and found the prevalence to be 36%, the highest of the 4 articles that reported it as a symptom.

Three articles reported the odds ratio of ocular symptoms. The overall pooled OR was 0.74 (95% CI: 0.45, 1.20; 95% PI: 0.45, 1.20). Heterogeneity was low with an I^2 of 0.0% (τ^2 = 0.00). A forest plot can be seen in Appendix 3.7, Figure 12. All articles recorded cough at the time of diagnosis/temporal artery biopsy.

3.5.5.23 Anaemia

Three of the articles included in this review reported findings on anaemia prior to a diagnosis of GCA. The overall pooled prevalence was 18% (95% CI: 10%, 27%; 95% PI: 7%, 32%) and heterogeneity was moderate, with an I^2 of 49.9% (τ^2 = 0.04). A forest plot can be seen in Appendix 3.5, Figure 22.

Two articles recorded anaemia at the time of diagnosis/temporal artery biopsy (Garrity et al., 2017; R. A. Stuart, 1989). Stuart et al (1989) recorded the prevalence of anaemia in their study sample as 36%. Garrity et al (2017) (a cohort study in the USA that has been described previously) reported the prevalence of anaemia as 19%. The remaining article (Hayreh et al., 1997) recorded clinical features at the time of referral to secondary care. This was a cohort study, also conducted in the USA, that used a positive temporal artery biopsy to identify patients with GCA. The reported prevalence of anaemia was 12%. The two articles conducted in the USA had similar prevalence estimates (12% and 19%), whereas the article conducted in New Zealand reported the largest prevalence of anaemia (35%).

3.5.5.24 Amaurosis Fugax

Five of the articles reported the prevalence of amaurosis fugax prior to a diagnosis of GCA. The overall pooled prevalence was 16% (95% CI: 6%, 30%: 95% PI: 0%, 50%), though heterogeneity was high, with an I^2 of 84.6% (τ^2 = 0.03). A forest plot can be seen in Appendix 3.5, Figure 23.

Three articles recorded amaurosis fugax at the time of diagnosis/temporal artery biopsy (Alba et al., 2011; Garrity et al., 2017; Abha G Singh et al., 2012). All three articles were cohort studies conducted in the Americas (Mexico and USA). They reported the prevalence of amaurosis fugax as; 27% (Alba et al, 2011); 15% (Singh et al 2012); and 27% (Garrity et al,

2017) respectively. Garrity et al (2017) used a positive temporal artery biopsy to identify GCA patients, whereas Alba et al (2011) and Singh et al (2012) used the ACR criteria.

The remaining two articles recorded amaurosis fugax at the time of disease onset (Kobayashi et al., 2003; Silva de Souza et al., 2013). Both articles were cohort studies, conducted in Brazil and Japan, with an overall pooled prevalence of 24% and 2%, respectively. This large difference in reported prevalence is most likely due to country of origin. Articles conducted in the Americas (Alba et al., 2011; Garrity et al., 2017; Silva de Souza et al., 2013; Abha G Singh et al., 2012) reported similar prevalence estimates of amaurosis fugax, ranging from 15% (Singh et al, 2012) to 27% (Alba et al 2011, Garrity et al 2017).

3.5.5.25 Cough

Four articles reported the prevalence of cough prior to a diagnosis of GCA. The overall pooled prevalence was 13% (95% CI: 3%, 28%; 95% PI: 0%, 49%). Heterogeneity between the articles was high, with an I^2 of 91.1% ($\tau^2 = 0.03$). A forest plot can be seen in Appendix 3.5, Figure 24.

Two of the articles recorded cough at the time of referral to secondary care (Desmet et al., 1990; Zenone & Puget, 2013). Both were cohort studies conducted in Europe and the prevalence estimates for cough were 35% and 14% respectively. Mean age was similar; however, the proportion of females in the sample differed at 74% and 67%, respectively. Zenone and Puget used the ACR criteria to identify patients with GCA, and Desmet et al (1990) identified patients with GCA through the clinical and histological information kept within a patient's file.

The prevalence estimate for cough produced by Zenone and Puget (2013) was closer to the prevalence estimate of 10%, found by Khalifa et al (2009) in their cohort study conducted in

Tunisia. Khalifa et al (2009) used a combination of the ACR criteria and positive temporal artery biopsy to identify patients with GCA. The final article recorded cough as a presenting feature of GCA on average 60 days prior to a diagnosis of GCA (Russo et al., 1995). This case-control study conducted in the USA reported the smallest prevalence of 2%.

3.5.5.26 Diabetes

Four articles reported the prevalence of diabetes prior to a diagnosis of GCA. The overall pooled prevalence was 13% (95% CI: 4%, 24%; 955 PI: 0%, 40%). Heterogeneity was high, with an I^2 of 93.2% (τ^2 = 0.02). A forest plot can be seen in Appendix 3.5, Figure 25.

Three articles (de Boysson et al., 2016; Espitia et al., 2012; Unizony et al., 2017) were cohort studies, with the remaining article being case-control (Pugnet et al., 2015). All articles were conducted in Europe, and conducted/published from 2010-present. Only 2 articles (de Boysson et al., 2016; Espitia et al., 2012) recorded diabetes at the time of diagnosis. Espitia et al (2012) reported the highest prevalence of diabetes, at 36%, using a combination of the ACR criteria and temporal artery biopsy to identify the 22 patients with GCA included in the study. De Boysson et al (2016) reported diabetes prevalence at 13% and used the ACR criteria to identify the 143 patients with GCA included in the study. Both studies were conducted in France.

The remaining articles (Pugnet et al., 2015; Unizony et al., 2017) reported the smallest prevalence estimates of diabetes (10% and 5%, respectively). Pugnet et al (2015) conducted a case-control study in France, using ICD-10 codes to identify patients with GCA. Diabetes was defined based on a record in the patient's file less than a month prior to the date of GCA diagnosis. Unizony et al (2017) conducted a cohort study in the UK, also using medical codes or prescription information to identify patients with GCA. Diabetes was defined based on a

record in the patient's file less than a year prior to the date of their GCA diagnosis. Mean age of the article populations and proportion of females included were similar between both articles.

3.5.5.27 Cerebrovascular accidents

Seven articles reported the prevalence of cerebrovascular accidents (CA) prior to a diagnosis of GCA. The overall pooled prevalence was 7% (95% CI: 2%, 13%l 95% PI: 0%, 26%). Heterogeneity was high with an I^2 of 92.7% (τ^2 = 0.02). A forest plot can be seen in Appendix 3.5, Figure 26.

One article (Ezeonyeji et al., 2011b) recorded CA on average 35 days prior to a diagnosis of GCA. Another article recorded CA between 1 and 12 months prior to a GCA diagnosis (Unizony et al., 2017). The remaining 5 articles recorded CA at the time of diagnosis/temporal artery biopsy.

Half of the articles were conducted in Europe, two in the UK (Ezeonyeji et al., 2011b; Unizony et al., 2017) and one in Spain (M.A. Gonzalez-Gay et al., 2005). All three used differing methods of diagnosis for GCA. Ezeonyeji et al (2011) used a positive temporal artery biopsy, Unizony et al (2017) used diagnostic codes and prescription information, and Gonzalez-Gay et al (2005) used the diagnosis given by Rheumatologists. All recorded CA at the time of diagnosis. Unizony et al (2017) reported the highest prevalence estimate for CA (22%), whilst the other article conducted in the UK reported a prevalence of 8%. However, the difference sample sizes between these two articles was large (6414 and 65, respectively). Gonzalez-Gay et al (2005) reported the prevalence of CA in their GCA patients as 2.5%.

The remaining studies were conducted in Israel, China, and Tunisia (Grossman, Barshack, KorenMorag, BenZvi, & Bornstein, 2016; Khalifa et al., 2009; Sun et al., 2016), and reported prevalence estimates of CA as 4%, 6%, and 3%, respectively. Despite being conducted in different countries these estimates were more similar to one another than the estimates from the articles conducted in Europe.

3.5.5.28 Diplopia

Eight articles reported the prevalence of diplopia. The overall pooled prevalence of diplopia was 6% (95% CI: 5%, 8%; 95% PI: 5%, 8%). Heterogeneity was low, with an I^2 of 0.0% (τ^2 = 0.00). A forest plot can be seen in Appendix 3.5 Figure 27.

Only one of the articles recorded diplopia at the time of disease onset (Kobayashi et al., 2003), whilst the remaining seven recorded diplopia at the time of diagnosis/temporal artery biopsy. Four of these seven articles were conducted in continental Europe (Duhaut, Pinede, et al., 1999; M A Gonzalez-Gay, Garcia-Porrua, Rivas, Rodriguez-Ledo, & Llorca, 2001; Gonzalez-Lopez et al., 2013; Haugeberg et al., 2000). The prevalence of diplopia in these articles were consistent at 5-6%. Three (Duhaut, Pinede, et al., 1999; M A Gonzalez-Gay et al., 2001; Gonzalez-Lopez et al., 2013) used either a positive temporal artery biopsy or the ACR criteria to identify patients with GCA, whilst Haugeberg et al (2000) used ICD-9 codes and a positive temporal artery biopsy. Overall these 4 articles produced similar results to each other.

The outlying article that produced a prevalence estimate that was largely different from the other articles was the cohort study conducted by Machado et al (1988) in the USA. The reported prevalence of diplopia in the 94 patients with GCA they identified was 12%. This study was conducted prior to the release of the 1990 ACR criteria, and so this article used a

combination of internally developed criteria and a positive temporal artery biopsy to confirm a GCA diagnosis. The other study conducted in the USA (Garrity et al., 2017) estimated the prevalence of diplopia on GCA patients with a positive temporal artery biopsy to be 8%. This would imply that diplopia may be more prevalent as a symptom in the American continent, however the remaining article which reported diplopia (Toren et al., 2016), conducted in Canada, produced a prevalence estimate more similar to those found in Europe (5%). The final article (Kobayashi et al., 2003) also produced a similar prevalence estimate of 6%.

3.5.5.29 Mental health conditions

Four articles reported the prevalence of psychological conditions. The overall pooled prevalence was 5% (95% CI: 1%, 12%; 95% PI: 0%, 19%). Heterogeneity was moderately high, with an I^2 of 72.4% (τ^2 = 0.01). A forest plot can be seen in Appendix 3.5, Figure 28.

Half of the articles were conducted in Europe (Desmet et al., 1990; Pugnet et al., 2015), in Belgium and France, respectively. Desmet et al (1990) conducted a cohort study, and recorded clinical features at the time of referral to secondary care. They identified patients with GCA using medical records. This article investigated mental deterioration, but gave no details as to what would constitute this diagnosis. They reported the prevalence of mental deterioration in the 34 patients prior to their diagnosis of GCA as 12%. Pugnet et al (2015) conducted a case control study, recording clinical features which had occurred less than a month prior to a GCA diagnosis. They used ICD-10 codes to identify patients with GCA. They recorded the proportion of patients who had a recorded diagnosis of dementia or psychiatric disorders, and these proportions were combined for the sake of this meta-analysis under the heading of psychological conditions. The reported prevalence was 2%. Continent of origin is the only variable these two articles have in common.

The remaining 2 articles (Khalifa et al., 2009; Kobayashi et al., 2003) were conducted in Japan and Tunisia, respectively. Kobayashi et al (2003) conducted a cohort study in which they recorded clinical features at the time of disease onset. Patients with GCA were identified using a positive temporal artery biopsy. They reported findings on psychiatric symptoms, and found a prevalence of 2%. Khalifa et al (2009) conducted a cohort study and recorded clinical features at the time of diagnosis. GCA patients were identified using a combination of the ACR criteria and a positive temporal artery biopsy. The reported prevalence of psychiatric manifestations was 10%.

3.5.5.30 Limb claudication

Four articles reported limb claudication as a clinical feature. The overall pooled prevalence was 3% (95% CI: 1%, 4%; 95% PI: 1%, 4%). Heterogeneity was low, with an I^2 of 0% (τ^2 = 0.00). A forest plot can be seen in Appendix 3.5, Figure 29.

All articles produced similar prevalence estimates of between 2.5% and 3%. Three articles were conducted in Europe (de Boysson et al., 2016; M.A. Gonzalez-Gay et al., 2005; Narvaez et al., 2003) whilst the remaining article was in China (Sun et al., 2016). All articles used either the ACR criteria, a positive temporal artery biopsy, or a combination of both to identify patients with GCA, and all recorded limb claudication at the time of diagnosis.

3.6 Discussion

The results of this systematic review and meta-analysis show that the clinical features which patients experience prior to their GCA diagnosis are extremely varied, and that the clinical features with the highest prevalence and strongest associations with GCA were headache, jaw claudication, constitutional/systemic symptoms, and elevated ESR. Features with strong evidence of a lack of association with GCA from the meta-analysis included PMR, and visual symptoms. However, there were many features including anorexia and fever where evidence is limited and more research is needed to fully understand the role (if any) of such clinical features prior to GCA diagnosis.

Headache was the most commonly experienced clinical feature prior to GCA diagnosis in this review, and whilst over three quarters of patients did experience this before GCA diagnosis, it is not a definitive precursor to eventually developing GCA. Prior to this review, estimates reported that a third of GCA patients did not experience a headache prior to their diagnosis, but that it is relied upon by GPs for diagnosis in primary care (Helliwell, Muller, Hider, Richardson, & Mallen, 2014). Though headache is clearly and commonly experienced prior to GCA, this is also a very common symptom in older patients. Whilst closely associated with GCA, and recommended as an indicating symptom in NICE guidelines, on its own in patients over 50 this could be indicative of a number of other conditions that are more prevalent in primary care populations, such as migraine or cancer (Prencipe et al., 2001; Rasmussen & Olesen, 1992), or a headache that is not associated with a disease (Boardman, Thomas, Millson, & Croft, 2005). This problem is highlighted by the fact that, despite the known association between headache and GCA, diagnostic delay persists.

When visual impairments, such as blindness and diplopia, are present with a headache, this is when GPs will typically become alert to a potential GCA diagnosis (Helliwell et al., 2014).

From this review, the overall pooled prevalence of visual impairment was less than half, suggesting that fewer GCA patients present with visual impairments than do not. Though this is a relatively small proportion of patients with GCA presenting with this symptom, it is a potentially serious and irreversible one. However, no significant increase in risk of GCA patients having a positive biopsy and presenting with visual symptoms was found in this review. This result could be due to "visual impairments" being a very broad definition and defined very differently between articles, or that patients may be consulting an optician rather than a GP, hence the visual impairment will not be in their medical record. Constitutional/systemic symptoms were defined with moderate consistency across articles. Some articles defined it as one symptom, such as pain or stiffness (Alba et al., 2011; Hayreh et al., 1997), whilst others included two or more symptoms such as asthenia, weight loss, and anorexia (M.A. Gonzalez-Gay, Garcia-Porrua, Llorca, Gonzalez-Louzao, & Rodriguez-Ledo, 2001; Gonzalez-Lopez et al., 2013). There were a number of papers which did not define it at all (El-Dairi et al., 2015; Grossman et al., 2016; Marí et al., 2009). Constitutional/systemic symptoms appear to be common in GCA patients, but are also a possible contributor to making the diagnosis of GCA more challenging. The definitions of constitutional/systemic symptoms was broad, and arguably they are not necessarily associated with a diagnosis of GCA. A patient may present with a fever prior to their diagnosis of GCA, but on its own this is not necessarily indicative of GCA, but possibly something else, like an impending cold. These symptoms highlight the disadvantage of considering clinical features independently of each other. Constitutional/systemic symptoms are a broad range of symptoms that even if grouped together would not necessarily be associated with GCA. Fever, weight loss, malaise, are all highly prevalent symptoms associated with a multitude of other, more prevalent, conditions from influenza to

malignancy (Wajngarten & Sampaio Silva, 2019). Grouping these symptoms under an umbrella term makes inference of a relationship between their presentation and a GCA diagnosis more difficult. Defining succinct combinations of these symptoms and investigating their association with GCA is an area for future research.

Elevated ESR had the second highest pooled prevalence, and was found to be strongly associated with a positive temporal artery biopsy. However, elevated ESR was only reported in 8 of the articles included in the review. What level of ESR was considered elevated differed between articles. One article defined it as >40 mm/h (E. Machado et al., 1988), whilst half of the articles defined it as ≥50 mm/h (El-Dairi et al., 2015; Marí et al., 2009; Mohamed & Bates, 2002; Rivero Puente et al., 2001). Only two articles did not give a cut-off value (T.A. Kermani et al., 2012; Toren et al., 2016). Elevated ESR is an inflammatory marker that can be an indicator of GCA (NICE CKS, 2020), but was not reported in many articles included in this review. This could be because blood tests may be conducted mainly in primary care, rather than secondary/tertiary care where all of the articles were conducted.

There has been little to no previous research that has investigated the association between anorexia and GCA. Anorexia was only reported in nine of the articles included in this review, but had one of the highest pooled prevalence estimates, with just over a third of patients reporting this feature prior to their GCA diagnosis. Only four articles reported a risk estimate, and the pooled odds ratio indicated there was a strong association between anorexia and a positive temporal artery biopsy. The articles that included anorexia did not provide a definition of anorexia, whether it was severe weight loss, or a loss of appetite. As a result of the findings in this review, future research should focus on further investigating the association between anorexia and GCA.

3.6.1 Heterogeneity

High levels of heterogeneity were consistently seen across the meta-analyses of clinical features, with articles included whose results consistently diverged from the other articles reporting the same clinical feature. The article by Desmet et al (1990) conducted in Belgium was consistently an outlier, and reported higher prevalence rates than other articles reporting the same clinical feature. It recorded higher prevalence rates of; constitutional/systemic symptoms, fatigue, anorexia, weight loss, fever, and cough; and a lower prevalence rate or jaw claudication. This article rated as fair on the N-O scale and included results from a small sample of thirty-four GCA patients. The method of diagnosis was patients who had either a clinical or histological diagnosis of GCA in their medical records in one single secondary care centre. This was one of the few papers in the review that recorded clinical features at the time of referral. It is not clear from the extracted information on this article why it would consistently report higher prevalence rates for six clinical features, but could be due to the small and possibly select sample used for this study. However, the prevalence estimates reported for other clinical features, such as abnormal temporal artery, visual impairment, PMR, and headache were all consistent with other articles, and close to the overall pooled prevalence rate. It is not possible to identify why the article by Desmet et al (1990) is inconsistent with other articles regarding some clinical features, whilst being an outlier in others.

The second article that reported higher prevalence estimates on some clinical features was an old study conducted by Fainaru et al (1979) in Israel on 47 GCA patients. This article was rated as fair on the N-O scale and identified GCA patients via a positive temporal artery biopsy from nine major hospitals. This study reported higher prevalence rates for; fever, visual impairment, and abnormal temporal artery. However, for the remaining clinical

features it reported (arthralgia, weight loss, fatigue, and headache), the prevalence estimates were similar to the overall pooled prevalence rate, and the prevalence reported in other studies. One other possible reason for these higher prevalence estimates could simply be because presenting features of GCA are different in the population studied in this paper. There were two measures of heterogeneity reported in this thesis, I^2 and τ^2. For the majority of meta-analysis both measures appeared to agree in terms of extent of heterogeneity. However, with τ^2 on a continuous scale, and no validated cut-off values, it was difficult to assess what value of τ^2 indicated high heterogeneity. Without the I^2 value as a comparator, it would have been difficult to identify where meta-regression was to be applied. In the cases where there was very high heterogeneity, indicated by an I^2 of over 95%, the value of τ^2 was variable and counter-intuitive. For example, the I^2 value for the meta-analysis conducted on articles reporting constitutional/systemic symptoms was the highest reported at 96.4%. Fifteen articles reported this clinical feature, and the resulting τ^2 value was 0.06. The meta-analysis with the second highest I^2 (ischaemic optic neuropathy at 96.3%) reported a τ^2 of 0.10 on the six articles that reporting ION. The difference in the values of τ^2, despite almost identical I^2 values, could be due to the precision of the studies included in each meta-analysis. Precision is proportional to the sample size of each study, and many of the studies included in the meta-analyses had small samples. I^2 is affected by precision, whereas τ^2 is not, making it a more stable and precise value. Regardless of this advantage over I^2, it still remains that τ^2 is difficult to interpret and will probably not be implemented as a replacement for I^2 in practice in the future.

What can be drawn from both I^2 & τ^2, is that the majority of meta-analyses conducted in this thesis had high levels of heterogeneity in prevalence estimates. In order to find the source of this heterogeneity meta-regression was conducted. However, the sources of heterogeneity

in the estimates of association could not be examined. No variable consistently explained heterogeneity in prevalence across the nine clinical features for which a meta-regression could be undertaken. However, continent of origin was included in the final model for constitutional/systemic symptoms, abnormal temporal artery, PMR, and fever. Year of publication was included in the final model for headache, constitutional/systemic symptoms, and abnormal temporal artery. This shows that for constitutional/systemic symptoms and abnormal temporal artery, a combination of geographical region and year of publication contributes to the differences in prevalence estimates between studies included in the meta-analysis. Heterogeneity associated with continent of origin could reflect differing models of healthcare in different countries. Affluent, or more developed countries, have increased access to healthcare technology and professional expertise than countries with a lower economic status. Year of publication may explain the differences between articles due to the slow progression on understanding and recognising GCA as a condition over time (G. G. Hunder, 2005). Articles conducted after the publication of the 1990 ACR criteria had the advantage of using it to classify GCA as a condition, in contrast to studies conducted prior which did not.

Overall the high levels of heterogeneity do not invalidate the results found in this review, but instead indicate wide variability in prevalence estimates and measures of association between studies. The results should be viewed with caution, and with the knowledge that there was a high amount of heterogeneity. There was little added benefit in using two measures of heterogeneity, and until τ^2 has been further developed regarding accepted cut-off values indicating high heterogeneity and used more widely in further systematic reviews, I^2 is the more accessible and easier to interpret measure of heterogeneity.

3.6.2 Comparison to previous GCA review

To date, only one other review has investigated the clinical features with which patients present prior to a GCA diagnosis. More specifically, they identified which features had predictive value of a positive temporal artery biopsy. The results reported by Smetana & Shmerling (2002) agreed with several of the findings found in this review, also finding headache, jaw claudication, and elevated ESR to be predictive of a GCA diagnosis. Smetana & Shmerling (2002) found a positive association between visual symptoms and GCA. However, this was not statistically significant, agreeing with the results produced in this thesis. Fever, weight loss, and fatigue (symptoms that were included in the definition of constitutional/systemic symptoms in this thesis) all had predictive value in the previous review, but only weight loss was statistically significant in this work. The prevalence estimates for anorexia, arthralgia, headache, jaw claudication, and PMR were similar in Smetana's review and the one conducted here. However, this review included more clinical features than Smetana's, and therefore provides a richer examination of experiences prior to a GCA diagnosis.

However, Smetana & Shmerling (2002) conducted their review on articles published from 1966 to 2000 in MEDLINE only (Smetana & Shmerling, 2002). The final number of articles included in their review and meta-analysis was 21, as opposed to the 43 included in this review. Smetana & Shmerling (2002) only included English-language articles, which may have introduced bias into their results. The use of MEDLINE only could have increased the possibility of missing relevant articles. Smetana & Shmerling (2002) also conducted their review almost 20 years ago, and the results from this review show that there is a difference in results depending on year of publication for certain clinical features, such as headache,

with those published between 1970 and 2000 having lower prevalence estimates than those published afterwards.

3.6.3 Strengths

The main strength of this review is that it is the first to conduct a meta-analysis on the relationship (prevalence and risk) between potential clinical features of GCA and a diagnosis, using 30 individual clinical features. This was a systematic search and identification of articles with no language filter, and articles were from a wide variety of countries. Another strength is the number of articles included in the final review. Suitable data to be used for a meta-analysis was extracted from a total of 43 articles, with the most frequently reported symptoms, such as headache, being extracted from 30 individual articles. Quality scores were validated independently by three reviewers and compared for agreement, reducing the amount of bias present in the results. A further strength was the relative consistency between articles regarding the method of GCA diagnosis. The majority of articles included in the review diagnosed GCA using a temporal artery biopsy, and all of the articles included in the measure of association meta-analysis used a temporal artery biopsy to define GCA.

3.6.4 Limitations

Despite the comprehensive review there is a possibility that some relevant articles were missed. Grey literature, such as theses, books, and unpublished material were not searched due to the likely benefits not outweighing the cost of time and resources required to conduct a search into multiple grey literature databases (Mahood, Van Eerd, & Irvin, 2014; Paez, 2017), and some articles were unable to be sourced.

The articles included in the risk estimate meta-analysis used biopsy results to define GCA and non-GCA patients, with the latter group defined as having a negative biopsy. However, all patients in these articles were suspected of having GCA when they were referred for a biopsy. Therefore it is reasonable to assume that measures of association based on comparing biopsy positive GCA cases, or GCA diagnosed patients, and the general population would be different to those found in this review comparing biopsy positive and negative patients.

It is a point of discussion whether the articles should be pooled together for a meta-analysis, considering very few were consistent in recording the duration of clinical features prior to a diagnosis. The largest subgroup was at diagnosis/TAB. Due to its large size, the pooled prevalence estimate for this subgroup was very close to the overall pooled estimate for all subgroups together. There was a high amount of heterogeneity found in the results for the meta-analysis conducted on the prevalence estimates. Some meta-analyses yielded large I^2 as high as 98%. A meta-regression was conducted to try to find the source of the heterogeneity. This is a useful model and should be applied to future meta-analyses that find high levels of heterogeneity between articles. Meta-regression, as well as explaining how much heterogeneity can be explained by the variables in the model, also has the ability to make comparisons of levels within the variables. In the case of this review, the meta-regression showed how the prevalence of a clinical feature differed between continent of origin or year of publication. A limitation was that meta-regression could not be conducted on the measures of association meta-analysis as there was not enough articles to include in the analysis.

The high heterogeneity between the results could not be fully explained by any of the covariates used in the models fit to the data. The results from the meta-regression showed

that no variable available from the data extraction was enough on its own to completely account for the high levels of heterogeneity, but did manage to explain a good proportion when combined with other covariates for some clinical features such as jaw claudication and fever. These results could mean that the high levels of heterogeneity observed in the proportion meta-analysis were due to a variable that was not recorded or not available to be extracted from the articles. Without further information it is difficult to come to a conclusion on the source of the heterogeneity across articles.

Sample size of articles included in the review were also a limitation. The majority of articles were conducted in single secondary care centres, and rarely reported outcomes on more than 100 patients, but this is to be expected with a condition as rare as GCA.

The timeline for when and how long patients had experienced clinical features prior to a diagnosis also varied across articles. The largest subgroup were the articles which had reported information on clinical features when the patient was being diagnosed with GCA, the “at diagnosis/TAB” group. These articles contained no information on the duration of clinical features prior to a diagnosis. This problem was shared with the “at referral” group whose clinical features had been recorded when they were referred onto secondary care or for a biopsy. There was no way to extract information from these articles about how long patients had experienced these clinical features, or how long it had taken them to be diagnosed from when they were referred. Together both the “at referral” and “at diagnosis/TAB” groups made up 36 out of the 43 articles included in this review. Arguably, the third largest group of “at disease onset” was also ambiguous regarding duration of clinical features prior to a diagnosis, as an amount of time from symptom onset to diagnosis was never specified in the articles (Kobayashi et al., 2003; Souza et al., 2013). Only 5 articles specified the duration of clinical features prior to a diagnosis of GCA (Ezeonyeji et al., 2011a;

Pugnet et al., 2015; Russo et al., 1995; Carlo Salvarani et al., 2004; Unizony et al., 2017). From the five, only 2 reported the same duration of 2 months/60 days prior to a diagnosis (Russo et al., 1995; Carlo Salvarani et al., 2004).

3.6.5 Conclusion

Diagnosing GCA based on the clinical features with which patients present with prior to GCA diagnosis can be challenging for healthcare professionals. This review has found that some "classic" features, such as headache, elevated ESR, and jaw claudication, are important indicators of GCA. However, even a high prevalence of an associated feature is of limited use if that feature is commonly seen across multiple conditions in primary care. The relationship between GCA and other features, such as systemic symptoms (including weight loss, fever, fatigue, malaise, and anorexia) needs to be further investigated. High heterogeneity between studies for many clinical features mean that further work is required to understand their prevalence and association with GCA.

Furthermore, the articles included in this review treated individual clinical features as though they were independent of each other, only looking at the effect of one at a time on a subsequent diagnosis of GCA. Previous articles have also shown that clinical features on their own do not always have high predictive value of a GCA diagnosis (Smetana & Shmerling, 2002). Identifying clinical features associated with a GCA diagnosis should include finding groups or clusters of clinical features that when presented together could identify a subsequent diagnosis, rather than treating features individually (Laskou et al., 2019). Observational data, such as that found in EHR, offers a large and representative sample size, and therefore reduces the lack of generalisability seen in small, single-centre secondary care studies that dominate this review. Hence the next chapter in this thesis will outline how

EHRs can, and will be used, to examine further the clinical features experienced by patients prior to their diagnosis of GCA.

Chapter 4: The Clinical Practice Research Datalink

4.1 Chapter Overview

This chapter gives a general overview of EHR databases, focussing specifically on details related to the Clinical Practice Research Datalink (CPRD) and how it was used to conduct the analysis included in this thesis to determine trends in prevalence and incidence of GCA, and clinical features associated with GCA. It describes how medical records are kept within the UK and stored in the CPRD database, CPRD's official processes of applying for data, the development of code lists for defining GCA and covariates, and finally the definition of the GCA study population used in this thesis.

4.2 Electronic Health Records (EHR)

In the UK, GCA is principally suspected, and managed over time in primary care (Helliwell et al., 2014), with referral to secondary care to confirm diagnosis. As a result, information on consultations, tests, and prescriptions are contained within the patient's primary care record. Primary care consultation data is therefore a practical resource to use in the UK for observational studies of GCA health care utilisation and management, including diagnostic and prognostic studies (Herrett et al., 2015).

4.2.1.1 Read codes

Diagnoses, symptoms, and processes of care in general practices have been recorded historically using Read codes and corresponding Read terms (Robinson, Comp, Schulz, Brown, & Price, 1997), the most commonly used hierarchical system of disease identification in UK general practice prior to the introduction of SNOMED coding from 2018 (Herrett et al.,

2015). Read codes were first developed in the 1980s to record clinical and administrative data in general practices. This first version is known as the four-byte set, as it used four-character alpha-numeric code, with each character denoting a level in the hierarchy. Version 2 was released to incorporate information from secondary and tertiary care, and was upgraded to a five-byte code to reflect this addition (Robinson et al., 1997). Version 3 was released in 1994 and was created through a collaboration between the National Health Service (NHS) Executive and the Conference Information Group of the Conference of Medical Royal Colleges; the Nursing, Midwifery and Health Visiting Professions; and the Professions Allied to Medicine (PAMS).

Read codes are organised via chapters 0-9, and then though chapters A-U (NHS Scotland, 2019). The numeric chapters record information on symptoms, examinations, investigations, and administration, whilst the alphabetical codes record information on diagnoses. Codes are hierarchical and version 3 allows for poly-hierarchy, rather than the 4 and 5 level limitations of previous versions. Top levels of the hierarchy are more general, and these become more specific further down the hierarchy (NHS Scotland, 2019). For example, one of the Read codes for GCA is G755. In this instance "G", defined within the Read chapter of circulatory system, is at the top of the hierarchy. At each addition of a number or other letter the diagnosis becomes more specific, and complex; such as G755z00 for "Giant cell arteritis – not otherwise specified", and G755100 for "Temporal arteritis" (Table 4.1).

Table 4.1: An example of the Read code hierarchy to arrive at the Read code for giant cell arteritis

Read code	**Read term**
G	Circulatory System
G7	Arterial, arteriole and capillary disease
G75	Polyarteritis nodosa
G755	Giant cell arteritis
G755z00	Giant cell arteritis – not otherwise specified

4.2.1.2 Availability for research

As of 2011, population estimates published by the Office for National Statistics (ONS) and the National Health Service (NHS) showed that 98% of the UK population were registered with a general practice (GP) (NHS, 2012). Information from these practices can provide data on patient consultations to primary care for many conditions, their presenting symptoms, diagnosis, and treatment pathways for the majority of the UK population, along with demographic information such as age, gender, and the level of socio-economic deprivation associated with the patient's local area (neighbourhood-level deprivation). As a result, there are electronic health databases available from several providers for use in research that contain pseudonymised information contributed by UK GP practices, such as registration information, diagnoses, prescriptions, results of tests, and referrals. Examples include The Health Improvement Network (THIN), the Clinical Practice Research Datalink (CPRD) (Petri et al., 2015; Unizony et al., 2017), QResearch (QResearch, 2020b), and ResearchOne (ResearchOne, 2020). All databases require approval from their research committees prior to the data being made available for research. Linked secondary healthcare data is also often available for researchers.

Established in 2003, and with data available from 1994 to the present day, THIN is an anonymised primary care record database from the UK, which contains medical data on 6% of the population (THIN, 2020). It contains information on patient demographics, diagnoses, referrals, prescriptions, and test results, from general practices that use the Vision software for the management of their EHR (Blak, Thompson, Dattani, & Bourke, 2011).

QResearch was developed jointly by the University of Nottingham and the Egton Medical Information Services (EMIS), a system used in many UK general practices to record patient data (Hippisley-Cox, Stables, & Pringle, 2004). It contains pseudonymised data from practices

that use the EMIS consultation system, and includes information on patient demographics, such as year of birth, sex, ethnicity, and Townsend Deprivation score (QResearch, 2020a). Linkage to national databases, such as the cancer registry, hospital episode statistics (HES), and the national death register, are also available. Currently QResearch contains information from approximately 1500 UK general practices (QResearch, 2020b).

ResearchOne collects information from health and social care organisations contributing to The Phoenix Partnership (TPP) SystmOne database (ResearchOne, 2020). TPP SystmOne has over 120,000 clients across more than 1900 GP practices in the UK, and is also used in secondary care departments such as Accident & Emergency (A&E) (ResearchOne, 2013). ResearchOne is created from records held in the TPP SystmOne from primary and secondary healthcare organisations in England. It is a pseudonymised database where healthcare providers have to opt-in for their data to be available to researchers.

THIN and ResearchOne are both smaller databases than CPRD and QResearch. ResearchOne only contains information from healthcare institutions in England and is therefore not suitable to use to investigate GCA in the UK as a whole. CPRD and QResearch are two of the largest databases in the UK. However, it was decided that the use of CPRD was the most appropriate approach for this thesis, not only because of the database size, but also because the host research institute for this PhD has familiarity with, and experience of using CPRD, and also has an institutional CPRD multi-study licence. A further benefit of using CPRD for this thesis is the quality checks that CPRD conducts on its database. CPRD has also been used for similar study designs in previous GCA research (Petri et al., 2015; Yates, Graham, Watts, & MacGregor, 2016).

4.3 Clinical Practice Research Datalink

Founded in 1987, CPRD is a government-owned research database that uses NHS primary care coded patient records contributed from practices across the UK (Jick et al., 2003). CPRD contains over 30 years of anonymised patient information from primary care that can be used for observational research. It contains patient information from, at the time of writing, over 1800 primary care practices from across England, Scotland, Wales, and Northern Ireland, and the covered patient population is generally reported to be representative of the UK population, based on age, gender, and ethnicity (CPRD, 2020a; Herrett et al., 2015; Wolf et al., 2019).

CPRD collects anonymised EHR from participating general practices on a monthly basis. Patients at registered practices are automatically opted-in to CPRD, but do have the option to opt-out of their data being included in the database. All patient data is psuedonymised, with the patient's name, address, postcode, and day and month of birth removed.

There are currently two databases contained within CPRD; GOLD and Aurum. The GOLD database contains information that has been gathered from general practices that use the Vision software to manage patient's medical records. The Aurum database was first released in 2017 and contains data from general practices that use the EMIS software (Booth & Dedman, 2017). Aurum has small differences in structure compared to GOLD, but still contains information in separate files on patients, referrals, drug issue, and consultation information, including the use of unique patient IDs that enable the files to be linked. At the start date of this study, the institutional licence only provided access to GOLD, with access to Aurum requiring an upgraded licence. However, access to Aurum is now included in the full institutional multi-study licence, but for the purposes of this thesis only data extracted from GOLD was used due to discrepancies between the two databases, detailed in section 4.3.1.2.

4.3.1.1 Structure & Contents

CPRD contains information on patients such as demographic data (year of birth, gender), lifestyle data (height, weight, smoking, and alcohol status), registration status (dates of joining/ leaving the general practice, and death), symptoms consulted with at each consultation, diagnoses applied, prescription information, immunisation information, referral records, and test results (Williams, van Staa, Puri, & Eaton, 2012).

CPRD data consists of separate tables all containing information about the practice or the patient, with each patient being allocated a unique non-identifiable ID number so they can be linked across all files. Patient demographics such as year of birth, gender, and important dates such as practice registration, transfer out, and death are in the table "Patient". Lifestyle information such as smoking status, alcohol consumption, and Body Mass index (BMI) are all contained within the "Additional" table. Information about consultations is contained within the "Clinical" table. Records of treatments, such as prescriptions of medications, are contained within the "Therapy" tables. Results of laboratory tests, like blood tests, are contained within the "Test" table. Details of patient referral to secondary care or specialists are contained within the "Referral" table.

Practice level data, such as up-to-standard date (see section 4.3.1.2), region where the practice is situated, and last collection date are all contained in the table "Practice". The 'last collection date' is the last date when data was collected from that practice, which can be used as a possible stop date for patients in studies, in conjunction with end of registration or end of study period. CPRD data is divided into 13 regions of the UK; 10 in England, and 1 each for Scotland, Wales, and Northern Ireland (Herrett et al., 2015). The 10 regions in

England are; East Midlands, East of England, London, North East, North West, South Central, South East Coast, South West, West Midlands, and Yorkshire and the Humber.

4.3.1.2 Quality & Validation

There are two quality checks conducted on CPRD GOLD data, one at the patient level and the other at the practice level. At the practice level there is an 'up-to-standard' (UTS) measure that indicates whether the data contributed by that practice is of a high enough standard to be used for research. The UTS date is a quality measure based on the practice's continuity of recording (gap analysis) and the number of recorded deaths in that practice (Herrett et al., 2015). Gap analysis is used by CPRD to identify any meaningful gaps in data recording at the practice. A meaningful gap is a single day, or longer, where nothing is recorded at the practice for a specific reason, such as if the practice was shut and patients were treated elsewhere. Gaps in the recorded dates of death at each practice are examined by CPRD, taking the population of that practice into account, in conjunction with seasonal and geographical variation in mortality rates (Herrett et al., 2015). Similar to the continuity of recording, if a significant gap is found in the recorded death dates, then the earliest date after which the gap occurred will be identified. The UTS date is taken to be the latest of these two dates for each practice (Herrett et al., 2015).

Regarding checks at the patient level, there is an acceptability flag. This is a binary variable that takes the value of 1 if the patient's data is of acceptable quality to be used in research. The criteria for acceptable patient data are:

1. To have a valid year of birth, gender, and age. Patients who have events before their date of birth, who are over 115 years old, or who do not have a gender identifier are unacceptable.

2. To have consistent and valid registration dates. The first registration date needs to be after the date of birth, and current registration (the same as the first registration date unless the patient has left the practice and returned at a later date) must be after date of birth.
3. To have a valid registration status. Patients without a permanent or temporary registration status are unacceptable. Patients must also have valid transfer out dates, if applicable, and reason to be considered acceptable.

Diagnosis validation studies have been conducted for CPRD. A systematic review identified 212 publications that validated diagnoses contained within CPRD (Herrett, Thomas, Schoonen, Smeeth, & Hall, 2010). From all 212 articles, over 183 different diagnoses were assessed for accuracy. Individual diagnoses are not listed in the article, but the results of a meta-analysis showed that overall validity of diagnosis was high, with a median positive predictive value (PPV) of 89%, with a range between 24% and 100% (Williams et al., 2012). The Aurum database, detailed in section 4.3, currently does not have the same dates recorded for patients as GOLD, such as the date of the last successful quality check and a validated death date. These dates were required to create a start and stop date for every patient included in this study. Therefore, it was not possible to have the same definition of start dates and end dates across patients in GOLD and AURUM, which would have affected the number of patients included in the analysis. It was decided by consensus that only GOLD should be used for this thesis. There is some overlap between the GOLD and Aurum databases as practices move from using Vision to EMIS.

4.3.1.3 Linkage

Data contained within CPRD is taken from general practices. However, a subset of included practices in England, approximately 58% of all UK practices within CPRD GOLD (Herrett et al., 2015), have consented to have their data linked to secondary care databases, such as Hospital Episode Statistics (HES), and the Index of Multiple Deprivation (IMD). For the purposes of this thesis only linkage to the IMD was required.

The Index of Multiple Deprivation (IMD) is an official measure of socioeconomic status calculated across small areas of England, usually referred to as Lower-Layer Super Output areas (LSOAs) (Department for Comminities and Local Governments, 2019). This information has been released by the UK Government since 2000, and updated versions were released in 2004, 2007, 2010, and 2015, with the most recent in 2019 (Department for Comminities and Local Governments, 2019). The LSOAs are designed to be of a similar population size, containing around 1500 people or 650 households each. LSOAs are ranked from 1 (most deprived) to 32,844 (least deprived) using the IMD (ONS, 2016). To create this rank value, the IMD is made up of seven individual Indices of Deprivation (IoD) which are weighted by:

- Income Deprivation (22.5%)
- Employment Deprivation (22.5%)
- Education, Skills and Training Deprivation (13.5%)
- Health Deprivation and Disability (13.5%)
- Crime (9.3%)
- Barriers to Housing and Services (9.3%)
- Living Environment Deprivation (9.3%)

Each of these indices is calculated from a range of Government data from the most recent time point available (Departments for Communities and Local Government, 2015).

4.3.1.4 CPRD Medcodes

CPRD uses medcodes to record patient information such as diagnoses, symptoms, and processes of care, with prodcodes used to record prescriptions. Medcodes are numerical codes that map to the Read code hierarchy, which can be done using the CPRD browser. This browser is part of the licence agreement with CPRD and is an application that can be used to search for Read terms, Read codes, and medcodes. The search results include the corresponding Read code/term, the medcode, and how many times it has been used in the current version of CPRD. Each Read code and associated term has a unique medcode. Prodcodes linked to prescribed medications can also be identified through the browser.

4.3.1.5 Strengths and limitations of the Clinical Practice Research Datalink

The large population in CPRD GOLD allows more statistical precision in results for rarer diseases than analyses run on a smaller set of data (Douglas et al., 2013). The median length of follow-up available in CPRD GOLD is 4.2 years for all patients, which allows research into the longer-term outcomes of diseases (Herrett et al., 2015; Wolf et al., 2019). It means that patients' healthcare use can often be followed from the period prior to the diagnosis, to longer-term follow-up. As it is routinely collected data, it does not have the same problems as questionnaire or survey data, such as non-response bias. Patients with records in CPRD GOLD are accepted to be representative of the UK population and therefore conclusions from CPRD GOLD research projects should be generalisable to the UK population as a whole in terms of age and gender (Herrett et al., 2015). CPRD carries out regular quality checks of its GOLD database, ensuring that the data used for research purposes is of the highest research quality (Herrett et al., 2015). CPRD also ensures that training in the recording of

patient information is given to practices contributing to GOLD to further ensure that data is of a high quality (Herrett et al., 2015).

A limitation of primary care data is that routinely collected data relies on Read codes to identify cases of a disease, and if the correct one is not used by the GP then the disease case will be missed in the analysis, or included when it should not be (e.g. a false positive). Information sent from secondary care may be added to a patient's record, but it has been shown that this is not always completed (Herrett et al., 2015). Multiple diagnoses and symptoms discussed in one appointment may not all be coded. A recent study found that on average 2.1 concerns were discussed per consultation (B. Stuart et al., 2019). A study was conducted to describe the differences between concerns discussed during a consultation, and those recorded in the patient's medical record (Salisbury et al., 2013). They found that across 229 videoed consultations, an average of 2.5 problems were discussed per consultation. They found that 72% of consultations were about multiple conditions. Of the 562 problems discussed across the consultations, only 37% were Read coded in the patient's file (Salisbury et al., 2013). However, the problem that is coded is likely to be the one of most importance to the patient and/or health care professional.

Another limitation of primary care records is missing demographic data, such as BMI, alcohol consumption, and smoking status. Reasons why data is missing varies, this results in different reasons for missingness and how they are handled prior to running analysis. For the purposes of this thesis only missing at random (MAR) and missing not at random (MNAR) will be discussed. MAR is where the missing data is missing due to other observed variables (Kang, 2013). MNAR is when the missing value is related to the reason it is missing, and this cannot be explained by the other variables in the data. Although routinely collected, there is evidence that some demographic information may not be collected for a specific reason

rather than a random instance, i.e. MNAR. BMI is one demographic that may be MNAR. Weight, used to calculate BMI, is more likely to be taken in women, patients who are older, or patients who look overweight (Bhaskaran, Forbes, Douglas, Leon, & Smeeth, 2013). Data that are MNAR are not suitable to be imputed by multiple imputation (MI) techniques as the results produced are biased (Sterne et al., 2009).

4.3.1.6 Independent Scientific Advisory Committee

A requirement before beginning a CPRD study is to obtain approval from the CPRD Independent Scientific Advisory Committee (ISAC), detailing a full protocol and analysis plan for the data. This protocol is submitted to ISAC so they can ensure the standard of studies using CPRD is maintained, and to ensure that the most appropriate methods are used to conduct the study using CPRD data (CPRD, 2020b). The ISAC application contains all the objectives for the project and details methods and specifics of the analysis to be carried out. Researchers must state in the ISAC to which databases linkage will be required. CPRD has ethics approval from the National Research Ethics Service Committee (NRES) for observational research only, as in the case for this thesis. Separate ethical approval is required for studies that directly involve contacting patients.

After the ISAC is submitted it undergoes internal peer-review. Any comments or changes suggested by the reviewers must be addressed to receive protocol approval. Only after the protocol has been approved by the ISAC can the data be accessed by the CPRD licence fob holder from the host department. A fob holder is a member of staff at the host department that accesses the CPRD databases for the data required for each approved ISAC protocol. If linkage to external databases is required, then this is completed by staff at CPRD.

4.4 GCA research in CPRD

CPRD has been used previously to investigate GCA (Durand & Thomas, 2012; Li et al., 2017; Li, Neogi, & Jick, 2018; Paskins et al., 2018; Petri et al., 2015; J. C. Robson et al., 2015; Smeeth et al., 2006), with the majority of studies investigating the association between GCA and other comorbidities after a GCA diagnosis. Durand & Thomas (2012) concluded that patients diagnosed with GCA have an increased risk of systemic infections within the first few months of diagnosis. Li et al (2017) concluded that patients with GCA were more likely than non-vasculitis patients to have vascular diseases prior to and after a diagnosis of GCA. Paskins et al (2018) concluded that patients with GCA had an increased fracture risk, and Robson et al (2015) found that patients with GCA have a twofold increase in risk of an aortic aneurysm after diagnosis.

Two of the largest studies to date were conducted by Smeeth et al (2006) and Petri et al (2015) and focused on the incidence and prevalence of GCA in the UK, jointly covering a twenty year period. Smeeth et al (2006) focused their study on the incidence and prevalence of GCA from 1990 to 2001. To be included as a GCA case, patients had to be 40 years or older, have a first diagnosis of GCA within the study period, and have two prescriptions of oral glucocorticoids; one within 6 months of the date of first diagnosis, and the second within 6 months of the first prescription, to indicate a clinical response to glucocorticoids. Diagnoses recorded within the first 6 months from registration were excluded from the analysis. This is because when a patient first registers at a practice any important or relevant conditions are often recorded by the doctor along with a relevant date. The date of the first GCA diagnosis can be subject to recall bias and may, therefore, be incorrect. Smeeth et al (2006) initially conducted a small validation study of GCA diagnoses in CPRD. In the UK, a GCA diagnosis is usually confirmed by a specialist, with the GP typically being informed by

clinical letter from the hospital after the patient has been referred there by their GP. These letters were requested from a sample of 50 patients who had a diagnosis of GCA in their primary care record. However, it was not stated whether these were a random sample. Of the 50 requested, 45 were obtained. It was found that the coding of GCA was supported in 91% of cases.

Smeeth et al (2006) identified 3298 patients who had a diagnosis of GCA in the study period and who met the inclusion criteria. The overall age-adjusted incidence rate was 2.2 per 10,000 person-years. The study found no increase in the incidence of GCA in the UK during the study period. They did find that a first diagnosis of GCA was more likely to happen in the summer months, and after a factor for seasonality was added to the analysis, it was found that this association was unlikely to be due to random error (Smeeth et al., 2006). The largest incidence rate was 7.6 per 10,000 person-years in women between the ages of 70 and 79 years.

Approximately a decade after Smeeth et al, Petri et al (2015) also modelled the incidence and prevalence of GCA using CPRD, but for a later time period, 2000 to 2011. They also investigated treatment pathways for GCA patients prescribed glucocorticoids (Petri et al., 2015). Their definition of a GCA patient was different from that used by Smeeth et al (2006). To be included as a GCA case, patients had to be 50 years or older at the time of diagnosis, have 1 or more Read codes for GCA in their record, and have 1 or more prescriptions of oral or systemic glucocorticoids at or within 6 months of the first diagnosis of GCA. Patients with a record of GCA in the first 6 months of their registration at the practice were excluded from the numerator because they were considered to be prevalent cases rather than incident cases.

Petri et al (2015) found 4671 cases of GCA after applying all of the inclusion criteria. Their overall incidence was 1.0 per 10,000 person-years in patients 50 years and over. They do not address why this value was half of that found by Smeeth et al (2006).

4.5 Overview of Methods

This section will briefly cover the development of code lists, the definition of the GCA study population, and information on the variables and files of CPRD GOLD that were used in the analysis within this thesis. The statistical software programmes R, R studio, and STATA were used to complete the data management and analyses (R Core Team, 2017; StataCorp., 2017).

4.5.1 ISAC

The ISAC protocol for this study, completed by LAB, was submitted in December 2018 and approved with no recommended changes in January 2019 (protocol number 18_315). The entire process, from starting draft protocol to approval took 11 months to complete. An amendment, indicating access to HES was no longer required, to the ISAC was submitted in October 2019 and approved in the same month (Appendix 4.1).

4.5.2 Code lists

In order to identify GCA cases a list of Read codes for a GCA diagnosis was compiled. Read code lists are developed to ensure that all cases are identified in the records as there is often more than one Read code that can be used to record a diagnosis. To define GCA, the CPRD code browser was searched for the terms “Giant cell arteritis”, “temporal arteritis”, and “GCA”. In the instances where previous publications (NHS, 2020; Petri et al., 2015; Springate

et al., 2014) had released their code lists for GCA, these were also checked and incorporated. A total of 5 Read codes relevant to a diagnosis of GCA were found and mapped to CPRD medcodes. The final list of GCA codes were approved by the supervision team (Table 4.2).

Table 4.2: Read codes and terms for all GCA related conditions, with mapping to the CPRD Medcode.

Read Term	Read Code	CPRD Medcode (GOLD)
Giant cell arteritis	G755	10432
Giant cell arteritis NOS	G755z00	68403
Temporal Arteritis	G755100	3275
Giant cell arteritis with Polymalgia Rheumatica	N200	29472
[X] Other giant cell arteritis	Nyu4100	53789

Code lists for symptoms and comorbidities (clinical features) to be investigated in the study were identified using the CPRD code browser (Appendix 4.2, Table 1). In addition, published code lists from previously published studies were also searched for relevant Read codes, with the corresponding medcode identified through the CPRD browser. For comorbidities such as hypertension, anxiety/depression, diabetes, and cardiovascular/cerebrovascular incidents, internally developed Read codes from the host department (https://www.keele.ac.uk/mrr/) were included in the final lists used for analysis. A prodcode list of glucocorticoid prescriptions had already been internally developed and validated in the host department. This list was thus used in this thesis (Appendix 4.2, Table 2).

4.5.3 GCA study population

Patients who had a GCA code recorded in their file between 1990 (start date of Smeeth et al, 2016) and end of 2017 (year of ISAC submission), who were 40 years or over and

contributing up to standard data at the time of first recorded diagnosis of GCA had their data extracted from CPRD by the fob holder. Start dates for each GCA case were defined as the latest of; the date the patient turned 40, the start of the study (01/01/1990), and the practice UTS date. End dates were defined as the earliest of; patient transfer out date, patient's date of death, the end of the study (01/01/2018), the date of last collection of CPRD data from the practice, and date of GCA diagnosis. A sensitivity analysis was also conducted where feasible where the GCA case definition was widened to incorporate prescription information on glucocorticoids. Patients had to have one or more prescriptions of glucocorticoids within six months after the first GCA diagnosis. A comparison of GCA case definitions between this thesis and the two previously published articles most relevant to the work conducted in this thesis can be seen in

Table 4.3.

Table 4.3: A comparison of GCA study population definition between this thesis and two previously conducted studies on GCA.

This thesis	Smeeth et al (2006)	Petri et al (2015)
Main analysis: • 40 years or older • Contributing UTS data • Diagnostic Read code for GCA Sensitivity analysis: • All of the above • One or more prescriptions of glucocorticoids within the first 6 months after first GCA diagnosis	• 40 years or older • Contributing UTS data • Diagnostic code for GCA • One glucocorticoid prescription within 6 months of first GCA diagnosis • A further prescription of glucocorticoids within 6 months of the first	• 50 years or older • N/A • Diagnostic Read code for GCA • One or more prescriptions for oral or systemic glucocorticoids at or within 6 months of the first GCA entry

This GCA study population was the basis for all further analysis in this thesis; investigating the association between clinical features and a subsequent diagnosis of GCA (Chapter 6), ascertainment of common patterns of clinical features prior to a diagnosis of GCA (Chapter 7), and for the next chapter, calculating incidence and prevalence rates in the UK (Chapter 5).

Chapter 5: The incidence and prevalence of GCA in UK primary care

5.1 Chapter overview

This chapter details the background, methods and results for an incidence and prevalence study of GCA in the UK using the Clinical Practice Research Datalink (CPRD).

5.2 Introduction

Incidence and prevalence data of conditions in any population is important information as this helps to inform relevant disease management, the allocation of healthcare funding, and resources for the investigation and treatment of any condition. The incidence and prevalence of GCA in the UK has most recently been examined by Petri et al (2015). Petri et al found an overall incidence of GCA of 1 per 10,000 person-years in patients 50 years and over from data taken from 2000-2011, in comparison to Smeeth et al (2006) who reported an incidence of 2 per 10,000 person-years in patients aged 40 years and over from data taken from 1990-2001. This difference between the two time periods of previous research shows the necessity for examining the entire time period, from 1990 onwards, to develop a clearer estimate of GCA incidence in the UK and how it is changing. The study by Petri et al concluded in 2012 (Petri et al., 2015)(Petri et al., 2015)(Petri et al., 2015)(Petri et al., 2015)(Petri et al., 2015) which leaves the most recent years' data relating to GCA unavailable to healthcare workers and officials and this is important given advances in investigative approaches and fast track pathways for suspected GCA, described in Chapter 2 section 2.3. Incidence is defined as how many new cases of a disease are recorded in a given period of time, usually on an annual basis (annual incidence). In contrast, prevalence describes how many cases there are overall, both new and existing, within a period (period prevalence) or

at a certain time (point prevalence). Previous studies into the incidence and prevalence of GCA have used primary care consultation data, as this is an available resource that details the information needed to calculate these figures based on patients presenting to healthcare, the subsequent findings are generalisable to the UK population, and allows geographical variation to be investigated. By using this data, it is possible to see how many patients had this condition recorded on their file and what treatment was prescribed. It is vital to know how prevalence and incidence changes over time so resources can be directed accordingly and training given where appropriate to manage these conditions suitably. This thesis will look at annual consultation incidence (the number of patients with the first recorded (coded) GCA diagnosis in primary care within a year), and the annual consultation prevalence (the number of patients with new or ongoing GCA, with a recorded (coded) diagnosis in primary care within the year).

5.3 Aims and objectives

The aim is to estimate the incidence and prevalence of GCA in UK primary care and model their trends over time. The primary objective is to determine trends in annual consultation incidence of GCA over time. The secondary objective is to determine the annual consultation prevalence of GCA.

5.4 Methods

5.4.1 Study design

A cohort study was conducted to examine the annual consultation incidence and prevalence of GCA in the UK and their trend from 1990 to 2017, using CPRD data. The consultation incidence was stratified by age, gender, and geographical region of the UK to allow for closer

examination and comparison between these factors. Age-standardisation was applied to the annual consultation incidence estimates using population data published by the Office of National Statistics (ONS). Finally, a sensitivity analysis was conducted to test the robustness of the definition used to define GCA cases.

5.4.1.1 GCA cases

As described in Chapter 4, section 4.5.3, for the primary analysis GCA cases were defined using only relevant Read codes. In a sensitivity analysis, the requirement was added that patients also needed a record of a glucocorticoid prescription alongside the GCA Read code, i.e. GCA cases had to have a Read code for GCA, and one or more glucocorticoid prescriptions within 6 months of first diagnosis (Petri et al., 2015). The start date for each case was the latest of;

1. The date the patient turned 40 years of age
2. The start of the study (01/01/1990)
3. The patient's practice's up to standard date
4. The current start of registration date plus 2 years

All four criteria were used to determine consultation incidence, whilst only the first three were used for consultation prevalence as the fourth was used to exclude prevalent cases when calculating incidence. End dates were defined as the earliest of;

1. Patient transfer out date
2. Patient's date of death
3. The end of the study (01/01/2018)
4. The date of last collection of CPRD data from their practice
5. The date of GCA diagnosis

5.4.1.2 Denominator population

The denominator population was all patients aged 40 years or over and who had passed the quality checks used by CPRD detailed in chapter 4 section 4.3.1.2. A start and an end date were also created for each member of the denominator population using the same definitions as described in section 5.4.1.1, with the exception of date of GCA diagnosis which is not applicable to the denominator population.

Files were merged to create one final dataset to be used for the consultation incidence analysis which contained demographic information for all eligible IDs (both GCA cases and general population). All data management was completed using R studio v3.5.2 (R Core Team, 2017).

5.4.2 Analysis

5.4.2.1 Consultation Incidence

To calculate the annual consultation incidence rates the numerator was the number of new GCA cases (i.e. patients aged 40 years and over with a first ever record of GCA) in a year (January-December), using the date of first GCA code recording as the index date. The denominator was total person-years (P-Y) at risk during that year, summed across everyone aged 40 years and over, with no prior record of GCA, and who contributed up-to-standard data during that year.

Crude and age-standardised consultation incidence per 10,000 P-Y were calculated annually with 95% confidence intervals from 1990-2017. Overall crude rates (from 1990-2017) were then stratified by age (40-49, 50-59, 60-69, 70-79, 80-89, & 90+), gender (male and female), geographical region (1-13 regions), age by gender, and region by year grouped into 5-year

increments (1990-1994…2015-2017). Age was categorised to allow comparison of consultation incidence by age, and 10 year increments were chosen as this has been used in previous UK incidence/prevalence studies of GCA (Petri et al., 2015; Smeeth et al., 2006). Age standardisation using UK population estimates for 2016, the most recent year's population data available taken from the ONS, was applied to the yearly incidence estimates. This was conducted so that the estimates from CPRD would reflect the UK population age-structure, thereby improving the generalisability of the consultation incidence estimates, and allowing fair comparison over time given that the age-gender structure of the population may change (B. Robson, Purdie, Cram, & Simmonds, 2007). All consultation incidence estimates and 95% confidence intervals were calculated using STATA v15 (StataCorp., 2017). All plots of consultation incidence were produced using the *ggplot* package of R v3.5.2 (R Core Team, 2017).

Following the descriptive approach described above, the independent association of the covariates with consultation incidence of GCA was modelled. There are two commonly accepted forms of modelling count/rate data. These are Poisson regression, and negative binomial regression. As the names imply, Poisson regression assumes that the response variable, in this case incidence rates, follow the Poisson distribution, whereas the negative binomial assumes the incidence rates follow a negative binomial distribution. The main difference between the two models is that the Poisson distribution assumes that the conditional variance and conditional mean are the same (Frome & Checkoway, 1985). This is not always appropriate and is dependent on the type of response data (UCLA, 2019). This assumption can be checked via a Pearson Chi-squared test (UCLA, 2019). This test checks the goodness of fit of the models. Previous studies into the incidence of GCA (Brekke et al.,

2017; Smeeth et al., 2006) have used Poisson models, hence for this study Poisson regression models will be fitted to the incidence data.

The covariates used were age (categorised into 10-year groups), gender (male and female), geographical region (1-13), and year (categorised into 5-year groups). The North East of England was set as the reference category for region as it is coded as number 1 in CPRD and lack of evidence that another region should be used as reference. The age group 60-69 was the reference category for age as there is evidence this is the age group where the incidence of GCA begins to rise (Petri et al., 2015).

5.4.2.2 Incident trends over time

To estimate the change in trends over time of annual GCA consultation incidence, joinpoint regression was used. This methodology is often used when the temporal trend is of interest (Doucet, Rochette, & Hamel, 2016; John & Hanke, 2015; Tyczynski, 2005). This methodology was chosen over time series methods (Wah et al., 2014) as it offers more information on where there are changes in trend which can help to identify events or policy changes that affect disease incidence.

Joinpoint regression was developed by the National Cancer Institute to model the trends in cancer mortality over time (National Cancer Institute, 2019d), but can be applied to measure the trend in most types of data (Rea et al., 2017). It fits the simplest joinpoint model that the data will allow (National Cancer Institute, 2019c). A joinpoint is the name given to the time point where there is a change in the underlying trend (National Cancer Institute, 2019d). There is some flexibility in regards to the number of joinpoints in the model, and the minimum and maximum to be assessed should be specified before fitting (National Cancer Institute, 2019c). However, the final number of joinpoints cannot be fixed beforehand (Rea

et al., 2017). The final number of joinpoints in the model are calculated from the available model selection criteria. For this study, three criteria were compared since there is no general consensus on which method provides the best model.

The first was the Monte Carlo permutation test method, this is done through a series of hypothesis tests (Rea et al., 2017). The simpler model, or the one with fewer number of joinpoints, is the null model, and the model with one more joinpoint is the alternative model. If the null model (starting with no joinpoints) is rejected, then the model with the greater number of joinpoints is chosen as the new null model. This step is repeated until the null model can no longer be rejected, and this model will be the final model (Rea et al., 2017). Permutation tests usually choose fewer joinpoints than other model selection criteria (National Cancer Institute, 2019b).

The second model selection method is the Bayesian Information Criteria (BIC), which is discussed in further detail in Chapter 7 section 7.4.2.1. The BIC is a common method of model selection that relies on Bayesian methodology to choose the best method (Posada & Buckley, 2004). The smaller the BIC the better the model.

The modified BIC (the third model used) was developed by Zhang and Siegmund (2007) specifically for change-point processes (Zhang & Siegmund, 2007). They argue that classic BIC does not work well in data with change-points due to the irregularities in the likelihood function. The Joinpoint model with the smallest BIC, or modified BIC is chosen (National Cancer Institute, 2019b). If all three model selection methods produced different joinpoint models then the most appropriate model would be reached via a consensus with the wider supervisory team.

The minimum and maximum number of joinpoints are dependent on the number of points (years) where there is data available: this can be specified by the user. The minimum

number of joinpoints was selected to be 0, as there was a possibility of there being no change in trend in the incidence data. The recommended maximum number of joinpoints for the number of years included in this study is 5 (years 1990-2017 = 28 datapoints) (National Cancer Institute, 2019e). Joinpoint surveillance programme v4.6.0.0 was used to fit the Joinpoint regression, for which the three methods of model selection were compared.
For every model the Annual Percent Change (APC) is calculated to interpret the change in trend over time (National Cancer Institute, 2019a). With this approach, rates are assumed to change each year at a constant percentage of the rate from the previous year. Each segment (i.e. time between two joinpoints) of the joinpoint model will have an APC value that may differ from other segments (National Cancer Institute, 2019a).

5.4.2.3 Consultation Prevalence

To determine annual consultation prevalence, the numerator was defined as the total number of people with at least one recorded GCA consultation during the year. Patients could only contribute one consultation of GCA per year. The denominator was the number of people aged 40 years and over registered at any point in the year and contributing up-to-standard data in CPRD during that year. Consultation prevalence was calculated annually. Age standardisation was completed on the annual consultation prevalence using the same methodology as applied to the annual consultation incidence, described in section 5.4.2.1.

5.4.2.4 Sensitivity analysis

A sensitivity analysis was conducted by including glucocorticoid prescriptions in the definition of GCA cases, to investigate if this would have an effect on the incidence rates. In the main analysis, only Read codes were used to define GCA cases. Previous studies (Petri et

al., 2015; Smeeth et al., 2006) have incorporated prescription information into their GCA case definition. For this thesis, to be eligible for inclusion in the sensitivity analysis, a patient with GCA had to have a Read code for GCA and one or more prescriptions for glucocorticoids within the first 6 months after a GCA diagnosis.

5.5 Results

5.5.1 Sample characteristics

The size of the total sample was 6,631,005 patients, which contained 9205 patients with a coded record of GCA and 6,621,800 without a record of GCA. 71% of the GCA patients were female and 52% of those without a record of GCA were female. The mean age at diagnosis for GCA patients was 72.6 years (SD = 10.3). For the sensitivity analysis, the total number of GCA patients was 8244; i.e. 89.6% of those with a GCA Read code also fulfilled the sensitivity analysis criteria.

5.5.2 Annual Consultation Incidence

The years with the lowest consultation incidence were 1990-1991, with 1990 having an incidence of 0.08 per 10,000 person-years (P-Y). Results tables for annual consultation incidence can be seen in Appendix 5.1, Table 1. There was an increase in the annual consultation incidence of GCA from 1990-1994, with a subsequent decrease in the annual consultation incidence from 1994 to 2001, and a further decrease from 2002 to 2017 (Figure 5.1). The year with the highest overall consultation incidence of GCA in UK patients 40 years and older was 1994, with an incidence of 2.29 (95% CI: 1.96, 2.67) per 10,000 P-Y. After age-standardisation was applied the consultation incidence rates did not greatly change (Figure

5.2). The results on consultation incidence from the sensitivity analysis were similar to the main analysis (Appendix 5.1, Table 2).

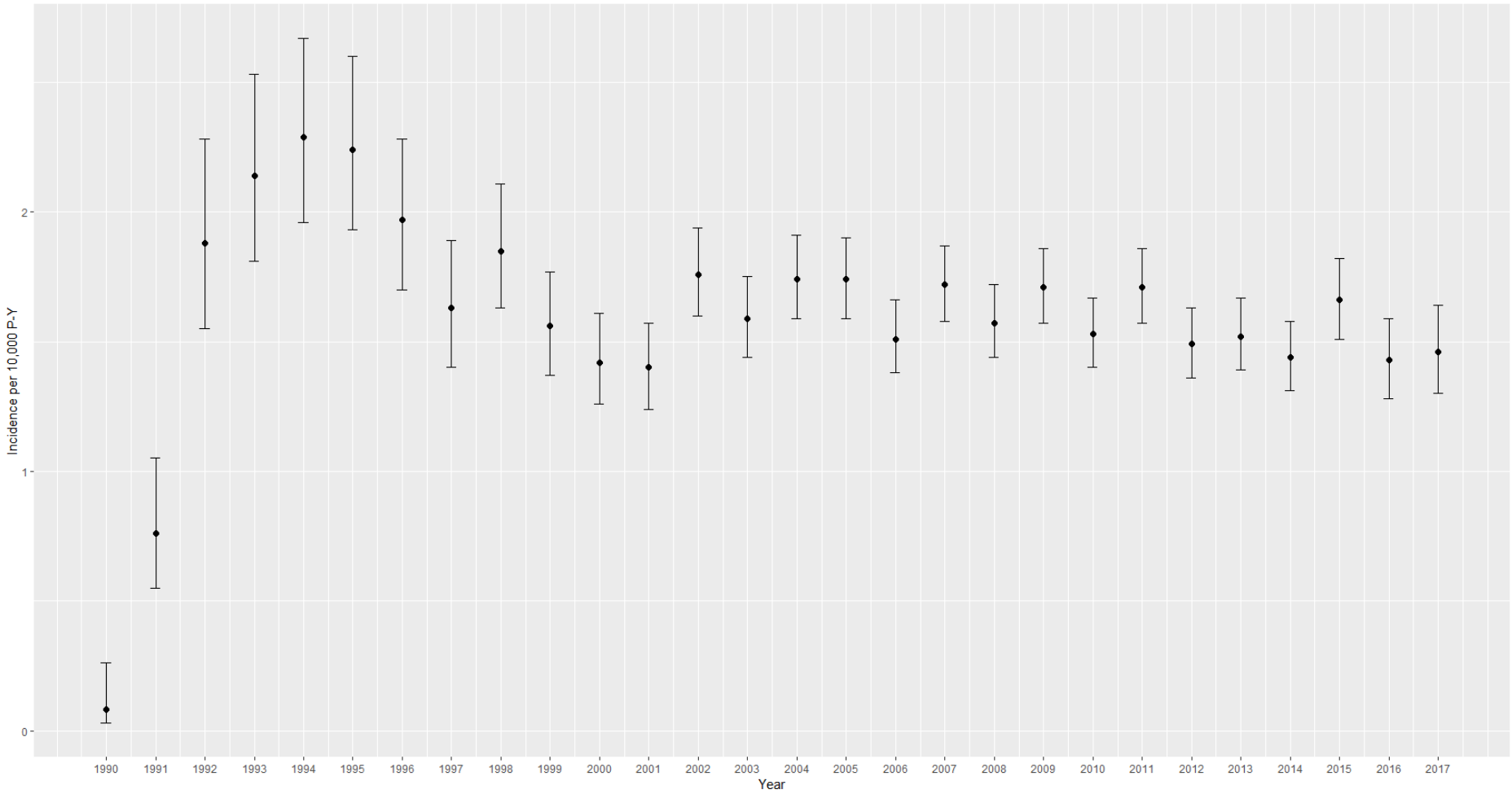


Figure 5.1: Annual incidence of GCA in the UK from 1990-2017.

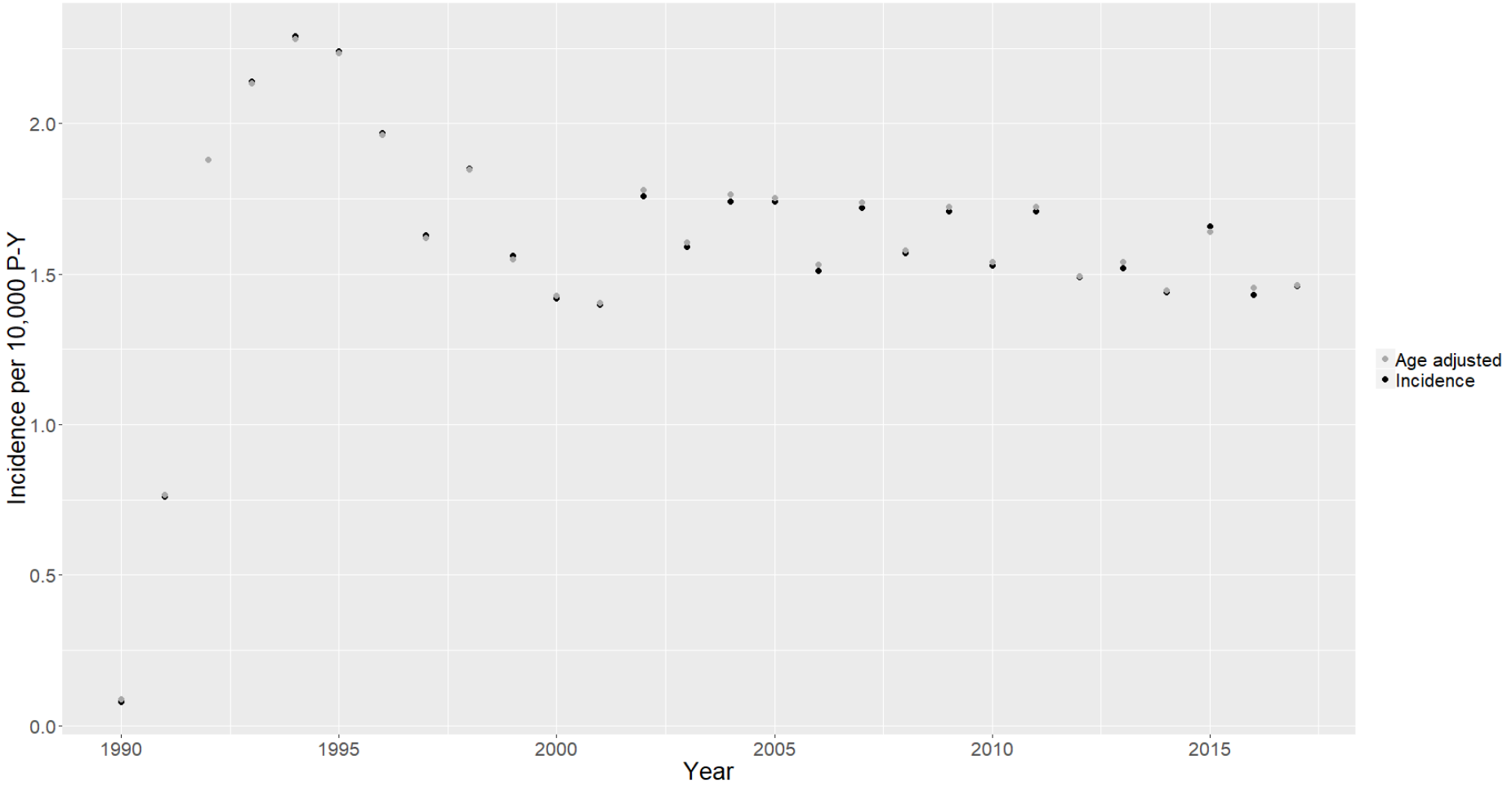


Figure 5.2: Annual incidence of GCA showing crude rates and age adjusted rates for 1990-2017.

Trends over time were assessed using joinpoint regression. The BIC model selection criteria suggested the optimal model had two joinpoints, placed at 1992 and 1999 (Figure 5.3). The trend from 1990-1992 was sharply increasing, but this is to be expected given these were the years with the lowest incidence rates. The incidence decreased from 1992-1999 by 5.68% per year, then by 0.31% per year from 1999-2017.

The resulting models from the permutation test and modified BIC can be seen in Appendix 5.1, Figures 1-2, respectively. The modified BIC model produced identical results to the Monte Carlo permutation test. These models resulted in 1 joinpoint at 1992, and assumed there was a constant decreasing trend of 1.46% per year from 1992-2017.

Due to the incidence in the years 1990-1991 being considerably lower than the rest of the time period, these were removed as probable outliers and the joinpoint regression model refitted using the same model selection criteria. The BIC (Figure 5.4) and the permutation test (Appendix 5.1, Figure 3) both suggested 3 joinpoints, at 1994, 2000, and 2004, as the optimal model. There was a sharp increasing trend from 1992-1994, with an increase in incidence of 10.73% per year, followed by a sharp decrease of 7.74% per year from 1994-2000. There was then another increase of 4.58% per year from 2000-2004, and then a shallow decrease of 1.20% per year from 2004-2017. The modified BIC (Appendix 5.1, Figure 4) result gave no joinpoints, and a constant decrease of 1.21% per year.

The preferred model, reached via discussion with the wider team, was fitted to the data from 1992-2017 and included 3 joinpoints (Figure 5.4), and was selected by both BIC and permutation test model selection. It indicates there is a potentially increasing trend between 2000 and 2004 that the other models miss.

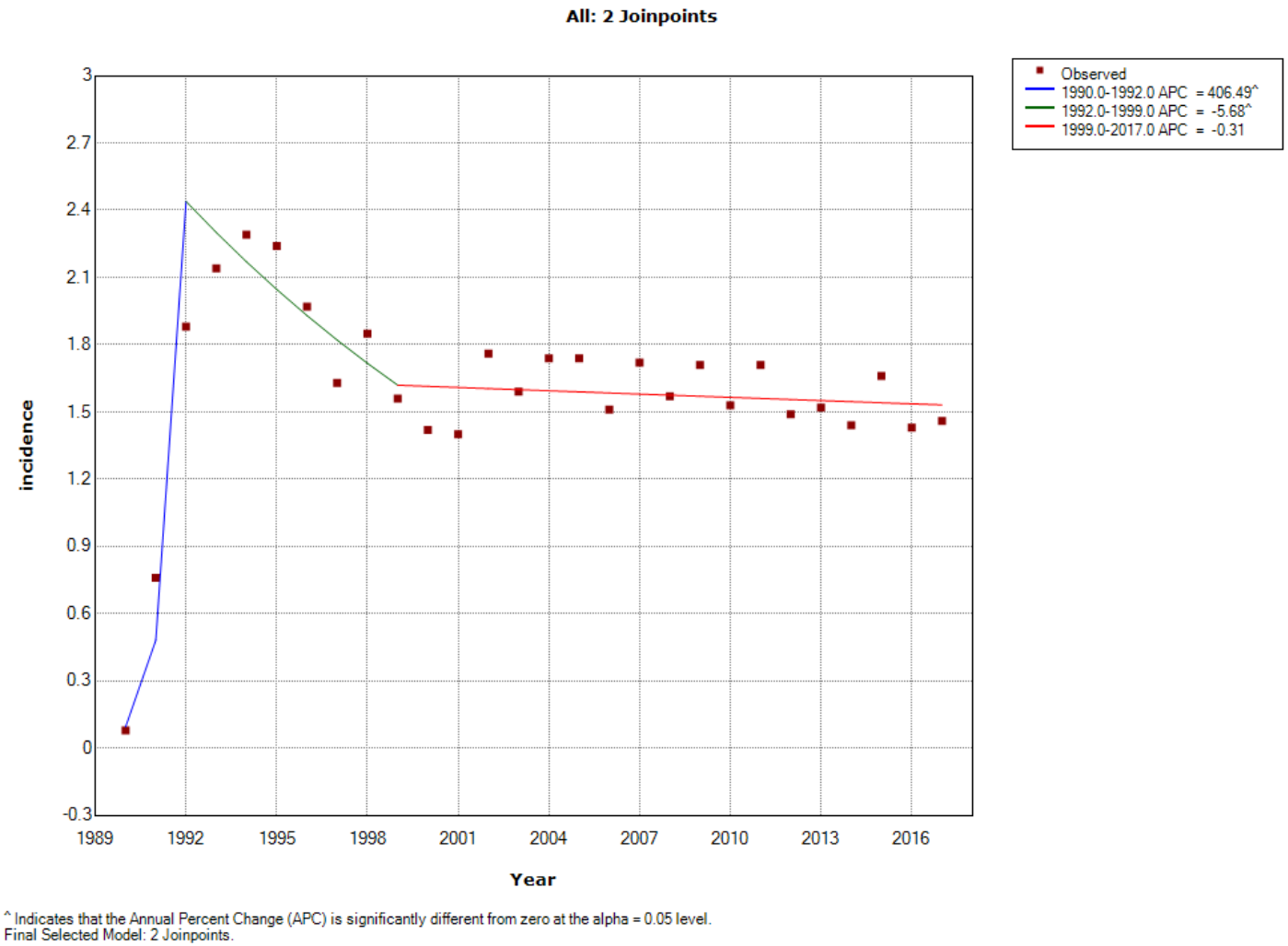
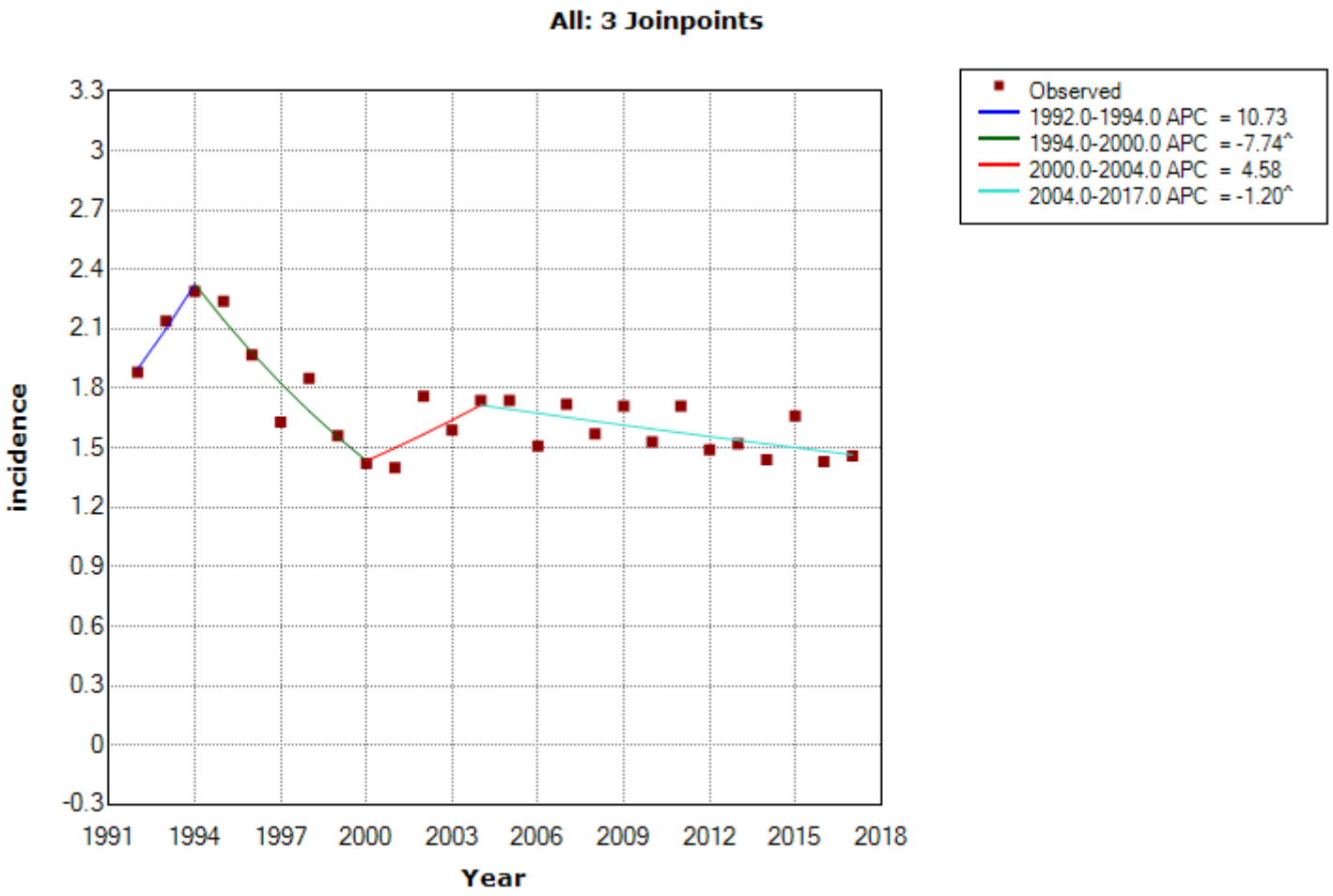


Figure 5.3: Optimal Joinpoint regression model using Bayesian Information Criteria (BIC) test showing 2 joinpoints.



^ Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
Final Selected Model: 3 Joinpoints.

Figure 5.4: Optimal Joinpoint model fitted on the years 1992-2017 with the BIC model selection.

5.5.3 Stratified incidence

5.5.3.1 Age

The consultation incidence rates from 1990 to 2017 were stratified by age. The highest incidence rate was observed in patients who were between 80 and 89 years (Table 5.1), with an overall consultation incidence of 4.30 per 10,000 person-years (P-Y) (95% CI: 4.10, 4.50). The lowest consultation incidence was for those aged between 40 and 49 years (0.15 per 10,000 P-Y, 95% CI: 0.13, 0.17). The results from the sensitivity analysis showed a similar pattern (Appendix 5.1, Table 7).

Table 5.1: Incidence of GCA per 10,000 person-years stratified by age, with 95% confidence intervals across all years.

Age (years)	**Incidence per 10,000 P-Y**	**95% CI**
40-49	0.15	(0.13, 0.17)
50-59	0.64	(0.60, 0.68)
60-69	1.90	(1.80, 2.00)
70-79	4.10	(4.00, 4.20)
80-89	4.30	(4.10, 4.50)
90+	1.70	(1.50, 1.90)

5.5.3.2 Gender

The annual consultation incidences for women were consistently higher than those for men, irrespective of year (Figure 5.5). All annual gender stratified incidence rates and corresponding 95% confidence intervals can be seen in Appendix 5.1, Table 3. When further stratified by age and combining all years from 1990-2017, females between the ages of 70 and 79 (Figure 5.6) had the highest overall incidence rate of 5.20 per 10,000 P-Y (95% CI: 5.0, 5.4). The highest incidence for men (3.10 (95% CI: 2.80, 3.40) per 10,000 P-Y) occurred between the ages of 80 and 89 years. Incidence was consistently higher for women across all ages (Appendix 5.1, Table 4). Results from the sensitivity analysis were similar (Appendix 5.1, Tables 8 & 9).

Figure 5.5: Annual incidence of GCA per 10,000 person-years, stratified by gender, from 1990-2017, with 95% confidence intervals.

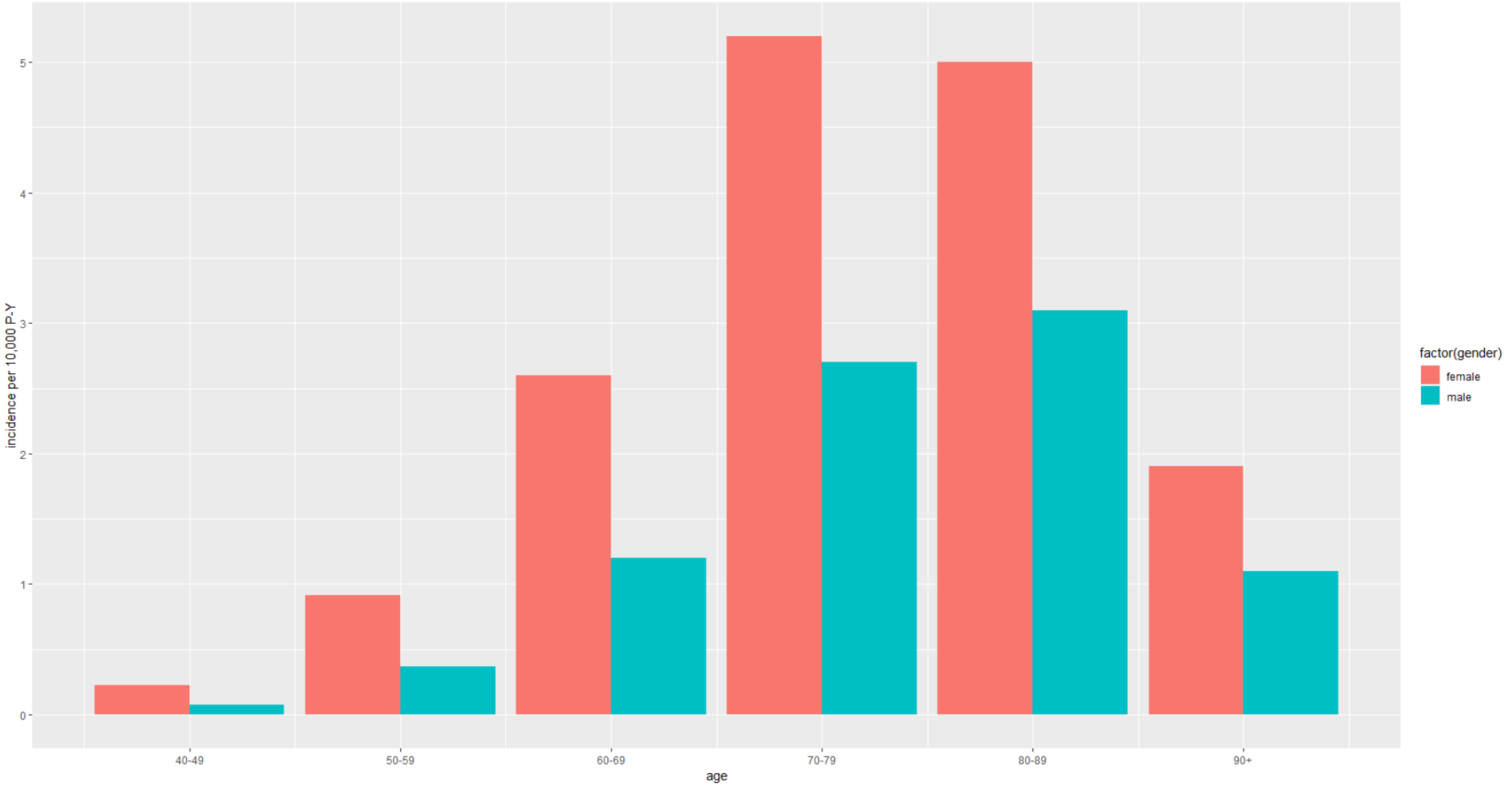


Figure 5.6: Incidence of GCA per 10,000 person-years stratified by age and gender.

5.5.3.3 Consultation Incidence rates by UK region

The region of the UK with the highest incidence rate of GCA between 2015 and 2017 (Figure 5.8) was Yorkshire & the Humber with 2.63 per 10,000 P-Y (95% CI: 1.49, 4.63). There were no practices from the East Midlands contributing data to CPRD after 2014 so this region could not be included in the analysis between 2015 and 2017. The regions with the lowest incidence (both 1.13 per 10,000 P-Y) between 2015 and 2017 were the North East (95% CI: 0.51, 2.51) and the West Midlands (95% CI: 0.85, 1.50). Incidence by region for years 1990-2014 can be seen in Figure 5.7 & Figure 5.8. There was little consistency in regional differences over the time-period, with every region having varying incidence rates across time points. The sensitivity analysis showed similar results (Appendix 5.1, Table 10).

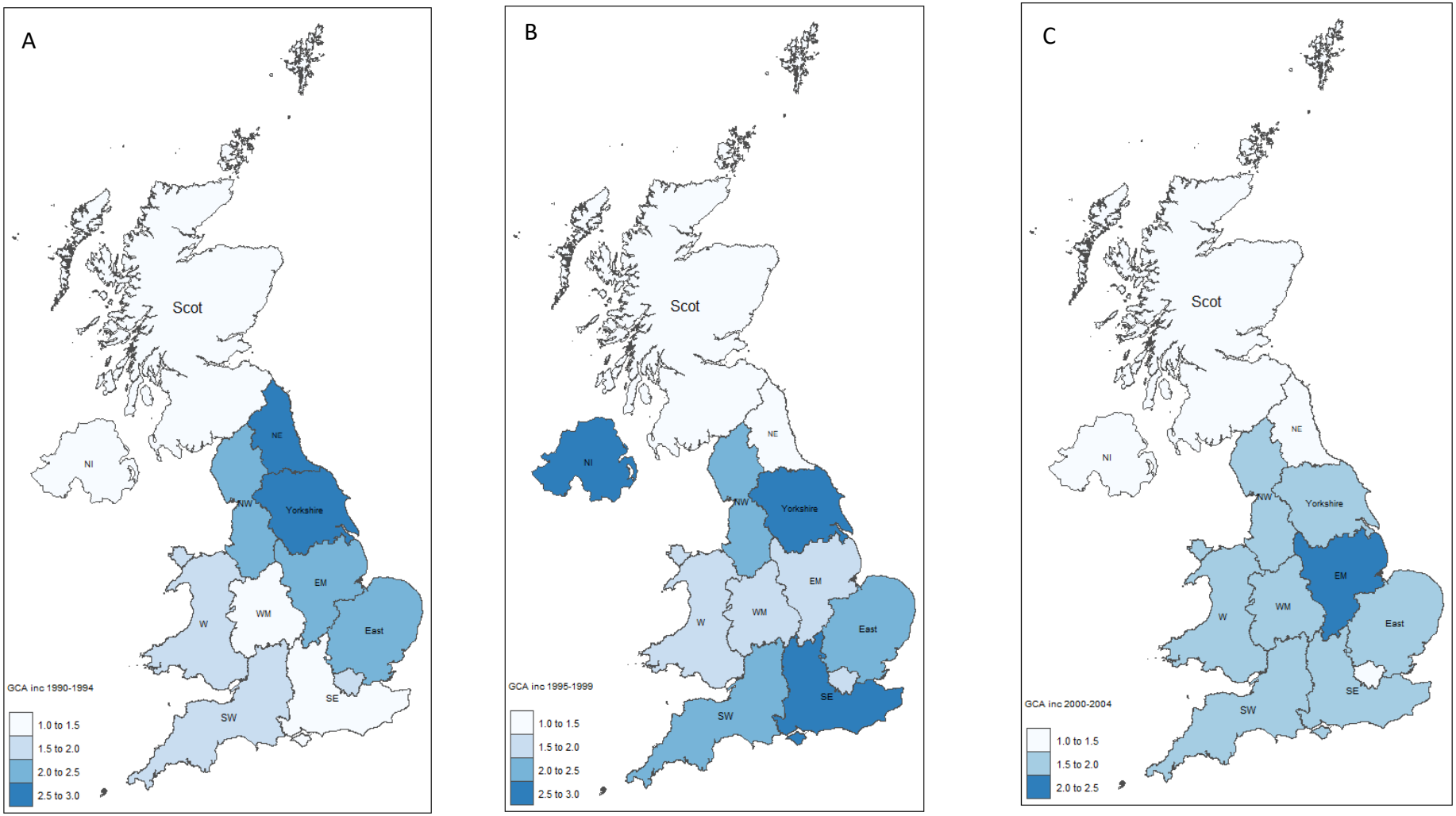


Figure 5.7: Incidence per 10,000 person-years map of the UK by each of the 13 regions included in CPRD for the years:

(A) 1990-1994; (B) 1995-1999; (C) 2000-2004

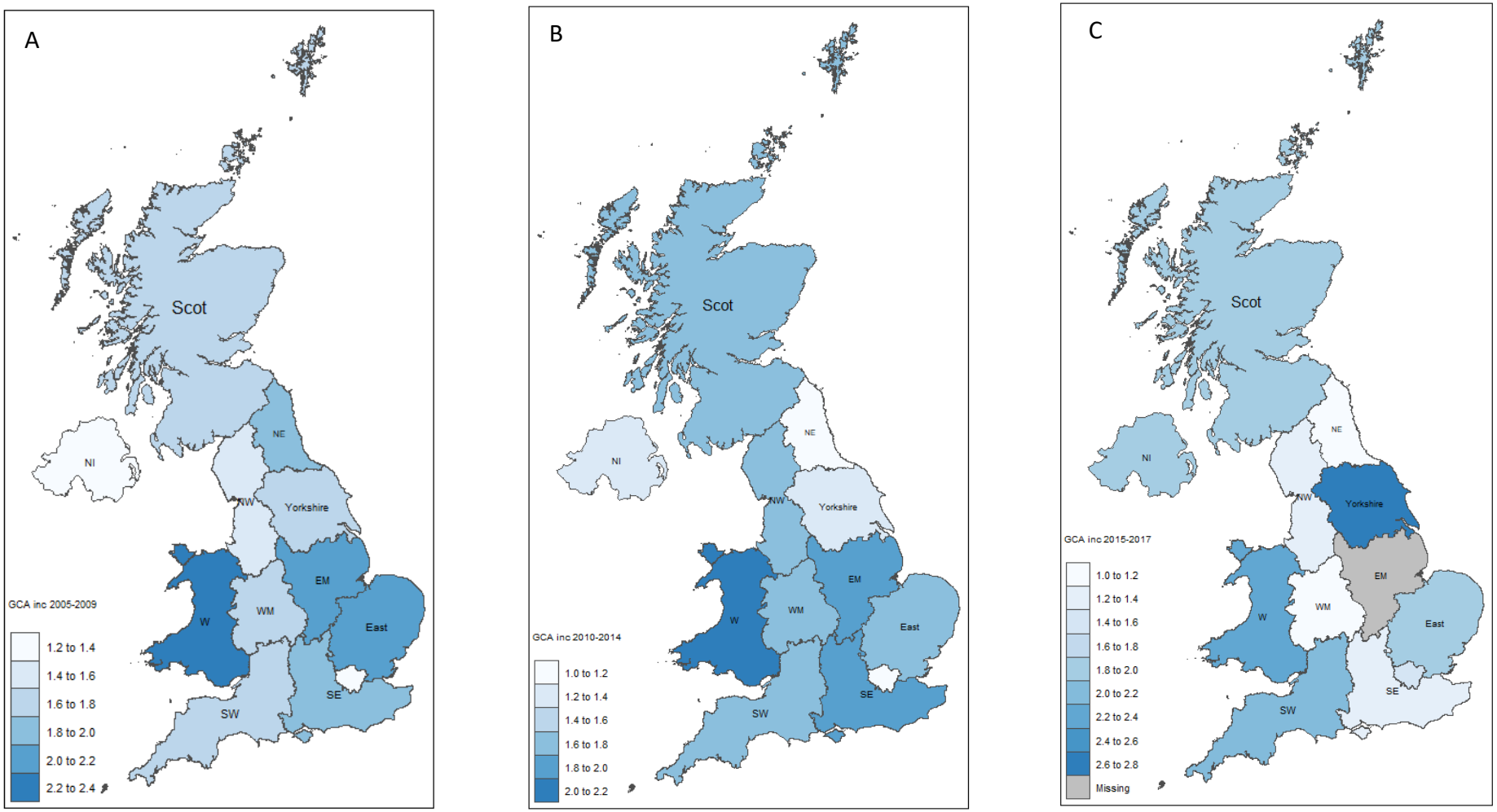


Figure 5.8: Incidence of GCA per 10,000 person-years map of the UK by each of the 13 regions included in CPRD for the years;

(A) 2005-2009; (B) 2010-2014; (C) 2015-2017

5.5.3.4 The association of covariates with consultation incidence

The unadjusted Poisson regression (Table 5.2) showed that females had a 2.21 times higher consultation incidence rate than males (95% CI: 2.11, 2.31), combining all years. London and Northern Ireland were the only regions of the UK with the suggestion of a decreased consultation incidence rate of GCA compared to the North East of England, with 15.1% and 5% decrease, respectively. However, these were not statistically significant.

In the adjusted model (Table 5.2) females had an almost double (95.6% higher) consultation incidence rate compared to males (IRR: 1.96; 95% CI: 1.87, 2.05). After adjustment for other variables, London and Northern Ireland continued to have a (non-significant) decreased consultation incidence rate when compared with the North East. Yorkshire and the Humber had a 29.1% increase in consultation incidence rate compared to the North East across all years 1990-2017. Age groups 40-49, 50-59, and 90+ years all had a significantly lower consultation incidence rates when compared with 60-69 years. Consultation incidence rate for 70-79 (IRR: 2.07, 95% CI: 1.76, 2.18) and 80-89 (IRR: 2.07, 95% CI: 1.95, 2.20) age groups were similar, and were more than 2 times higher than the consultation incidence rate for 60-69 years.

Table 5.2: Incidence rates of GCA in the UK, by covariate.

Covariate	Unadjusted IRR	95% CI	Adjusted† IRR	95% CI
Female	**2.206**	**(2.109, 2.307)**	**1.956**	**(1.870, 2.047)**
Region				
North East	Ref		Ref	
North West	1.138	(0.950, 1.364)	1.140	(0.951, 1.365)
Yorkshire and The Humber	**1.333**	**(1.094, 1.624)**	**1.291**	**(1.059, 1.574)**
East Midlands	**1.360**	**(1.115, 1.658)**	**1.335**	**(1.094, 1.629)**
West Midlands	1.044	(0.869, 1.254)	1.019	(0.848, 1.224)
East of England	**1.293**	**(1.077, 1.551)**	**1.277**	**(1.064, 1.532)**
South West	**1.209**	**(1.008, 1.449)**	1.125	(0.938, 1.349)
South Central	1.016	(0.847, 1.218)	0.972	(0.811, 1.166)
London	0.849	(0.703, 1.024)	0.915	(0.758, 1.104)
South East	1.163	(0.971, 1.394)	1.118	(0.933, 1.340)
Northern Ireland	0.950	(0.773, 1.169)	0.993	(0.807, 1.221)
Scotland	1.044	(0.871, 1.251)	1.086	(0.906, 1.303)
Wales	**1.366**	**(1.143, 1.633)**	**1.319**	**(1.104, 1.578)**
Age				
40-49	**0.077**	**(0.068, 0.088)**	**0.080**	**(0.070, 0.091)**
50-59	**0.331**	**(0.306, 0.358)**	**0.338**	**(0.312, 0.365)**
60-69	Ref		Ref	
70-79	**2.128**	**(2.018, 2.244)**	**2.068**	**(1.761, 2.181)**
80-89	**2.216**	**(2.087, 2.353)**	**2.072**	**(1.951, 2.200)**
90+	**0.742**	**(0.648, 0.850)**	**0.683**	**(0.596, 0.782)**
Year				
1990-1994	0.894	(0.799, 1.001)	0.921	(0.823, 1.031)
1995-1999	Ref		Ref	
2000-2004	**0.888**	**(0.821, 0.960)**	**0.871**	**(0.805, 0.941)**
2005-2009	**0.915**	**(0.850, 0.985)**	**0.898**	**(0.833, 0.967)**
2010-2014	**0.854**	**(0.793, 0.920)**	**0.854**	**(0.792, 0.921)**
2015-2017	**0.846**	**(0.775, 0.924)**	**0.890**	**(0.814, 0.974)**

† Adjusted for female, region, age, and year.
Significant results in bold.

5.5.4 Consultation Prevalence

The highest annual consultation prevalence (Figure 5.9) was observed in 1995 with 6.86 people consulting with GCA per 10,000 P-Y (95% CI: 6.28, 7.48). From 1995 onwards the annual consultation prevalence ranged between 4 and 6 per 10,000 P-Y. The trend in annual consultation prevalence is almost identical to the trend found for annual consultation incidence. A table of annual consultation prevalence estimates can be found in Appendix 5.1, Table 5. After age-standardisation was applied (Appendix 5.1, Table 6), the highest consultation prevalence remained in 1995 with 6.83 per 10,000 P-Y (95% CI: 6.24, 7.45).

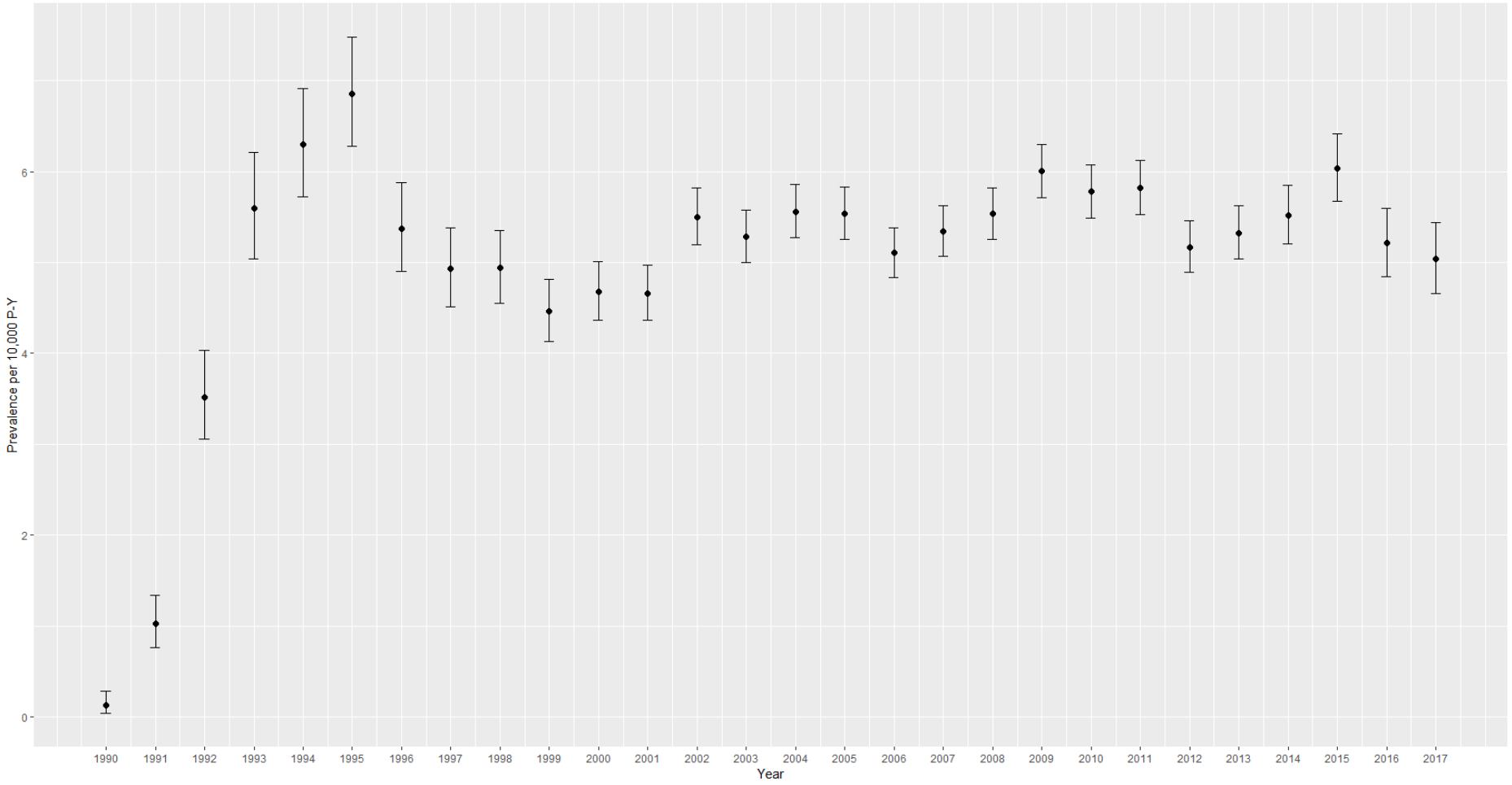


Figure 5.9: Annual consultation prevalence for GCA per 10,000 person-years for 1990-2017.

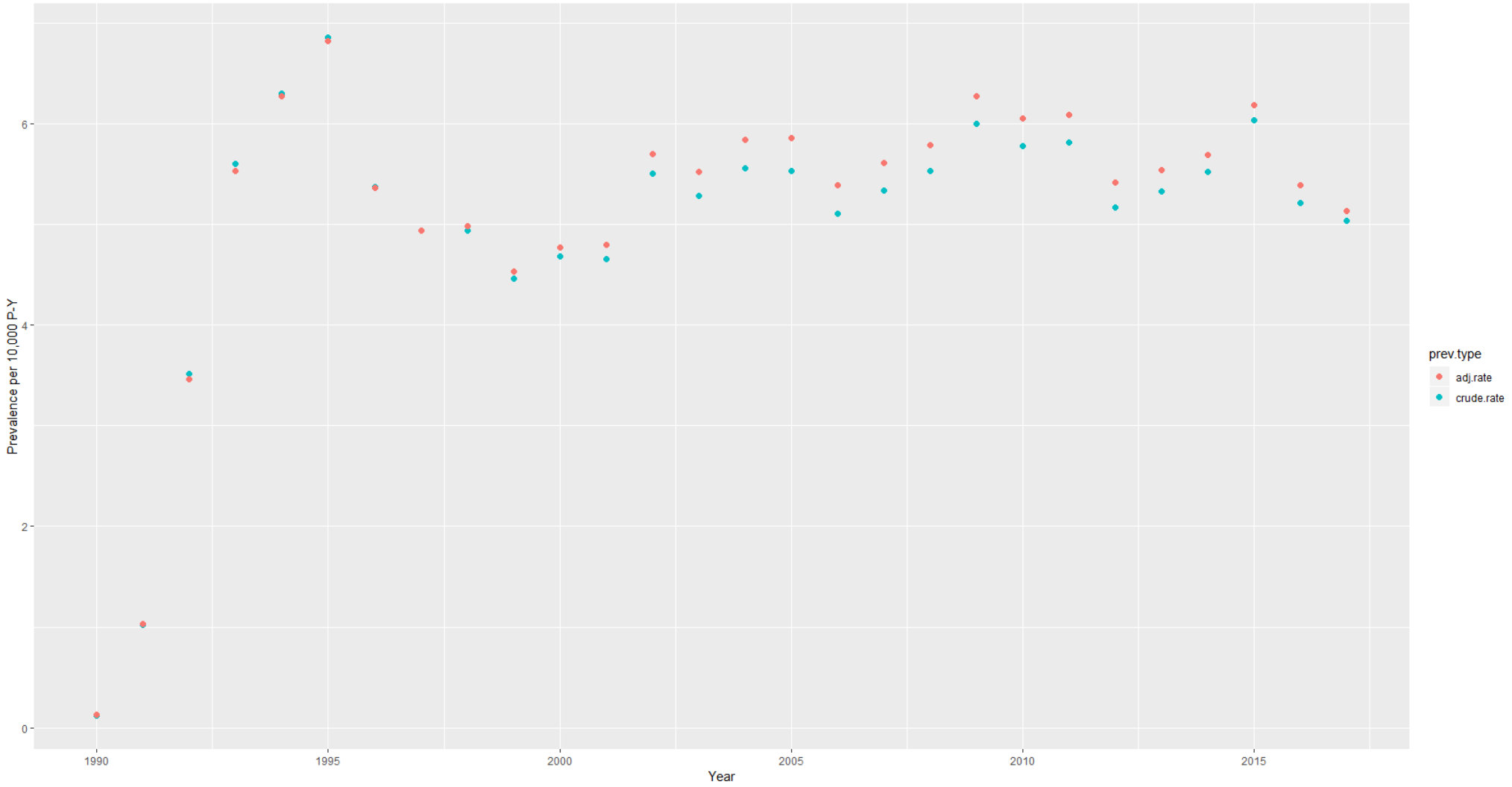


Figure 5.10: Plot of crude consultation prevalence and age-adjusted consultation prevalence for years 1990-2017.

5.6 Discussion

This large national study of patients with GCA has shown that the annual incidence of GCA in the UK has gradually decreased from 1992-2017, except for a small increase between 2000 and 2004. Females across all ages have consistently higher incidence of GCA than men, with those aged between 70 and 79 having the highest overall incidence. Between 2015 and 2017 the region of the UK with the highest incidence was Yorkshire and the Humber. After age-standardisation was applied, the crude and adjusted incidence rates were very similar. The annual primary care consultation prevalence of GCA in the UK has gradually decreased from 1996 to 2017, with small variation between years.

5.1.1 Trend of GCA in the UK

When investigating the trend in GCA incidence, it became clear that there were three time points where the trend in GCA consultation incidence changed between 1992 and 2017. In 2000 the trend changed from decreasing to increasing, until 2004. There does not appear to be any clinical reason for this sudden change in trend as there is no obviously known changes to medical guidelines regarding the management or treatment of GCA in these years. The trend again changes in 2004, and continues to decrease for the rest of the time period, until 2017.

The incidence rates from 1990-1992 are very small, compared to the incidence rate for years 1993-1995 which are the highest of the entire time period. One reason for these results is the 1990 ACR criteria. Prior to the release of these criteria there was very little research published concerning GCA, and few clinical features that were reported to be associated (Gene G. Hunder et al., 1990). It could be that the low incidence estimates observed between 1990 and 1992 were due to a lack of recognition and understanding of GCA as a

condition in primary care, and the increase in incidence from 1993-1995 is an overcompensation, or is during a wave of GCA research following the release of the ACR 1990 criteria. This may be a similar reason for the increase in incidence between 2000 and 2004.

These changes in trend were all captured by the Joinpoint model. Different methods of model selection were used and compared to identify which produced the best model, both statistically and clinically. The final model, which included 3 joinpoints that reflect the changes in trend as described above, was selected by two of the three model selection criteria that was applied in the analysis. After discussion with the supervisory team, it was decided that this model best described the changes in trend seen in the data, without overfitting. The model that was produced by the final model selection criteria (modified BIC) was deemed to be under-fitted, as it missed the small change in trend from 2000-2004.

5.6.1 Comparison to other literature

There have been two previous studies investigating GCA in the UK population using electronic health records. The study by Smeeth et al. (2006) investigated the incidence of GCA (defined as Temporal Arteritis) between 1990 and 2001. The overall age-adjusted incidence rate for the entire time-period was reported as 2.2 per 10,000 P-Y. They did report a small decrease in the incidence over this time-period, identical to the trend found in the same time period in this thesis. As with this study, females at each age group, from 40 years to 80+ years had consistently higher incidence rates of GCA than males. Smeeth et al (2006) found that the age standardised incidence rates varied by region of the UK, showing that GCA was more common in the south from 1990 to 2001. The results from this thesis found

variation in the incidence rates between regions with no discernible North/South pattern. Scotland did have consistently lower estimates than certain regions of England.

The second study was by Petri et al (2015) and was conducted on data from 2000 to 2011. Incidence rates were stratified by age and gender. Annual incidence rates of GCA were not reported in the article. The overall incidence rate of GCA reported by Petri et al (2015) was 1.0 per 10,000 P-Y. Again females had a higher incidence rate of GCA than males, with the highest incidence in females aged between 70 and 79 years.

There were a few small differences between the two articles and this thesis. All three had slightly different eligibility criteria for GCA cases to be included in the analysis. For instance, Smeeth et al (2006) required 6 months of prior registration at a practice to be eligible, whereas this thesis required 2 years. Regardless of differing eligibility criteria, the populations should be similar enough to draw some comparisons (Table 5.3).

Table 5.3: Comparison of methods and patient eligibility between the two previously published articles on the incidence of GCA in the UK using CPRD, and this thesis.

	Smeeth et al (2006)	Petri et al (2015)	This thesis
GCA case eligibility criteria	• Aged 40 years and over at first GCA diagnosis • Read code for GCA • Contributing UTS data • A prescription of glucocorticoids within 6 months of first GCA diagnosis • A second prescription within 6 months of the first	• Aged 50 years and over at first GCA diagnosis • Read code for GCA • Contributing UTS data • One or more prescriptions of glucocorticoids within the first 6 months of GCA diagnosis	• Aged 40 years and over at first GCA diagnosis • Read code for GCA • Contributing UTS data • (Sensitivity) One or more prescriptions of glucocorticoids within 6 months of first GCA diagnosis
Years included in analysis	1990-2001	2000-2011	1990-2017
GCA Read codes used	Not reported	G75500, G755.00, G755z00, N200.00, G755100	G75500, G755.00, G755z00, N200.00, G755100, Nyu4100

A comparison between annual incidence rates can only be conducted between this thesis and Smeeth et al (2006), as Petri et al (2015) did not report these results. Overall, the incidence rates in this thesis were smaller than those in Smeeth et al (2006). The main difference between results lies in prior registration required for all GCA cases to be included in the analysis. As mentioned, Smeeth et al (2006) required 6 months of prior registration at a practice to be eligible, in contrast to the 2 years required in this analysis. This could mean that more prevalent GCA patients were included in the Smeeth et al (2006) analysis than in this thesis, hence the smaller consultation incidence estimates produced in this thesis. Comparison of incidence rates by age is possible between this thesis and Smeeth et al (2006); however, Petri et al (2015) only included age-gender stratified incidence rates and presented these results in a figure. Similarly to the annual incidence rates, the incidence rates from 1990-2001, stratified by age, are lower in this thesis than those reported by Smeeth et al (2006), but show a similar pattern. The incidence of GCA in patients younger than 70 years is low, with an increase after the age of 70 years. Incidence rates for the age groups from 40 years to 70 years were similar between Smeeth et al (2006) and this thesis. The main divergence came for the age groups 70-79 years and 80-89 years. However, both studies showed that these two groups had the highest incidence rate when compared to younger age groups. Comparisons can be made between the incidence rates stratified by both age and gender. As mentioned previously, Petri et al (2015) only reported these results in a figure. However, estimates of the incidence rates can be derived from the figure. The incidence rate of GCA by age and gender between this thesis and the two previous articles show a similar pattern. All show that females aged between 70 and 79 years have the highest incidence rate for GCA in the UK. As with previous comparisons between incidence rates of GCA between studies, the incidence rates in this thesis are smaller to those

published by Smeeth et al (2006) and Petri et al (2015), possibly due to differences in GCA case definition. However, all show a similar pattern. That females have consistently higher incidence rates of GCA, and that the highest incidence rate is observed in patients aged 70-79 years.

The final comparison can be made between regions of the UK. Smeeth et al (2006) found that the age standardised incidence ratios were larger for regions in the south of the UK. Results from this thesis showed that in the years of the Smeeth et al study (1990-2001), southern and eastern regions of England had the highest GCA incidence rates. Smeeth et al (2006) also found that Scotland had a much lower GCA incidence rate than the rest of the UK, a finding which was also found in this thesis. There was no discernible pattern found between regions of the UK from 1990-2001.

5.6.2 Strengths and limitations

The biggest strength of this study is the scope of the analysis, with over 25 years and over six million patients included, and over 9000 with a diagnosis of GCA. Both previously published studies have completed analysis on available data, usually a period of 11 years. This study includes data on more than double that period, at 27 years, from 1990 to 2017 and allows for continuity of data as these years were all included in the same analysis. This breadth of information has allowed the use of Joinpoint regression methodology to investigate how the trend of GCA in the UK has changed. No study has previously modelled the trends in incidence of GCA in the UK using Joinpoint regression in a primary care electronic health record setting, hence this approach is novel in UK primary care research.

The main limitation of this study were the annual incidence estimates seen for the years 1990-1992. These appeared to be outliers, and were greatly different to the rest of the

years. This could be due to differing definitions of GCA cases between this study and those published previously, and hence all three studies including a different number of GCA cases (Petri et al., 2015; Smeeth et al., 2006). A previous study (Jordan et al., 2007) which used CPRD to estimate annual consultation prevalence of musculoskeletal (MSK) conditions in CPRD also showed that the consultation prevalence was lower in 1991 for all MSK conditions than those calculated using other primary care databases for the same year. The authors theorised that this low prevalence could be due to not every consultation for chronic conditions being coded in a patient's record (Jordan et al., 2007; Porcheret et al., 2004). It is possible that the coding of GCA in the early years of CPRD had a similar problem.

As a result, to model the trend of GCA these years were removed for a sensitivity analysis. Most importantly the trend model for 1993 to 2017 did not change when these were removed. In the case of incidence, the data from years 1990 to 1992 were noticeably lower to any other year. This could be due to poorer data quality in these years, lack of quick communication between secondary care where GCA patients are diagnosed and primary care health providers, or a lack of patients with the required 2 years of prior registration. Alternatively, CPRD may have applied quality checks to historical data from these years, which may have excluded patients as their data would not be of sufficient quality to include in research. The reason for the discrepancy in the years 1990-1992 can only be hypothesised. Previous studies into the incidence and prevalence of GCA in the UK have used a 6 month prior registration period (Petri et al., 2015; Smeeth et al., 2006), whereas in this study patients had to have 2 years of prior registration before they were included in the analysis.

Another limitation is connected to the use of CPRD. Although GCA diagnosis in CPRD has been validated (Smeeth et al., 2006), this does not mean that every case of GCA is

successfully coded to a patient's record. Since a GCA diagnosis is confirmed in secondary care, there may also be a delay in communication between primary and secondary care, hence the date of diagnosis of GCA can be incomplete in a patient's record (Herrett et al., 2015; Smeeth et al., 2006). However, the number of GCA patients not included in the analysis for this reason would, in all likelihood, not affect the overall results found in this thesis.

5.6.3 Conclusion

This chapter has established the most up to date consultation incidence and consultation prevalence estimates of GCA in the UK. Overall, the trend in new cases of GCA is decreasing slowly and the greater presence of disease continues to be seen in women and the oldest. Not only has this chapter established the extent to which GCA is a problem in UK primary care, but also defined the study sample that will be used in the following chapters. The next steps are to improve understanding of the association of symptoms and comorbidities that present prior to a diagnosis of GCA, and to assess their relationship and magnitude contributing to a subsequent diagnosis.

Chapter 6: Associations of presenting clinical features and a diagnosis of GCA

6.1 Chapter overview

This chapter details the methods and results for conducting a case-control study investigating the association between the clinical features with which patients present in UK primary care and a subsequent diagnosis of GCA using the Clinical Practice Research Datalink (CPRD).

6.2 Introduction

Previous studies investigating the clinical features which patients present with prior to a diagnosis of GCA have mainly been single centre and conducted in secondary care settings. The systematic review conducted in Chapter 3 showed that these studies did not consistently identify clinical features related to a subsequent diagnosis of GCA. Despite the review results indicating that headache, jaw claudication, anorexia, and constitutional symptoms were highly prevalent and associated with a diagnosis of GCA, there remained limitations due to many clinical features also being commonly observed in other conditions, unexplained heterogeneity in prevalence, and strength of associations with GCA between studies, variation in definitions of GCA diagnosis and clinical features, the point of measurement of these features, and lack of evidence for other clinical features. This review highlighted the need for a broad, rigorous study that used a more generalisable sample of patients set within primary care to investigate the relationship between the existence of clinical features, and the point at which these are consulted for, and subsequent diagnosis of GCA.

6.3 Aim

The aim of this study is to quantify the association between the presenting clinical features of GCA and a subsequent diagnosis of GCA and to investigate the time from feature onset to GCA diagnosis.

6.4 Methods

6.4.1 Study population

Patients diagnosed with GCA (defined in Chapter 5) from 1990-2017 were used as the cases for a case-control study. The control population were patients registered with a practice contributing to CPRD who were aged 40 years and over, and who did not have any record of a GCA diagnosis.

GCA cases were matched to controls by their general practice, gender, and exact year of birth, on a ratio of 1:5 cases to controls. Whilst increasing the number of matched controls improves efficiency and the precision of the effect estimate, it has been shown that this improvement is minor in a ratio of more than 4 (Kuo, Duan, & Grady, 2018). Incomplete sets were permitted, i.e. if five matches could not be found for every case, a minimum ratio of 1:1 cases to controls was used (Hamajima et al., 1994; Hennessy, Bilker, Berlin, & Strom, 1999). Matching is a commonly used method to adjust for confounding prior to analysis. Patient demographics such as age, gender, and general practice are most commonly used as matching factors as these are important confounders and results can be influenced if they differ significantly between the case and control population (Kuo et al., 2018; Wacholder, Sllverman, Mclaughlin, & Mandel, 1992).

Each case-control set had an index date assigned. This was the date of GCA diagnosis for the case in each set. Every consultation (GP visit that had been assigned a Read code) after the

index date was removed from the data before analysis, since this study was only investigating clinical features recorded prior to or on the same day as a GCA diagnosis. This included any recorded BMI, smoking, or alcohol consumption status.

6.4.2 Clinical features

As part of the ISAC process detailed in Chapter 4, code lists for each of the clinical features found in the systematic review (Chapter 3), were created using the CPRD and Read code browsers, published Read code lists from previous studies, validated Read code lists created and used by the host department (School of Medicine), or input from the supervisory team. These lists included mapping of Read codes to CPRD medcodes (Appendix 4.2). Lists included individual codes for other conditions, such as cardiovascular/cerebrovascular diseases, along with all codes associated with specific clinical features such as headache, anorexia, and visual impairment.

If a clinical feature had been included in the review and/or meta-analysis, (Chapter 3, sections 3.5.4 & 3.5.5), then it was eligible to be included in the case-control study if relevant Read codes could be found. A total of 14 clinical features were investigated: headache, weight loss/anorexia, fever, fatigue, visual impairment, elevated ESR, cardiovascular/cerebrovascular conditions, hypertension, anxiety/depression, PMR, diabetes, jaw pain, and any cancer. Patients with each clinical feature were identified if the Read code for the clinical feature had been used in their record. Read codes used to define each clinical feature can be seen in Appendix 4.1, Table 1.

Headache, visual impairment, PMR, and elevated ESR were all clinical features that were reported in a large proportion of the articles included in the systematic review (Chapter 3, section 3.5.5). Headache and visual impairment are also viewed as “classical” symptoms of

GCA and particularly relevant in primary care settings, from which CPRD draws its data, due to them being easily recognisable (Helliwell et al., 2018). Regarding PMR and elevated ESR, the review conducted in Chapter 3 showed a pooled prevalence of 34% and 76%, respectively, and positive association between elevated ESR and a diagnosis of GCA. Elevated ESR was defined as a recorded ESR value of ≥50 mm/h, a cut-off value used by the majority of the articles in the systematic review.

Currently there is no Read code for jaw claudication, a symptom that has been shown to be highly associated with a diagnosis of GCA in the systematic review conducted in Chapter 3. Jaw pain was the closest term to jaw claudication that was available in the Read code hierarchy, and after discussion with the wider supervisory team, it was decided that this would be the code most likely used if a patient presented with jaw claudication.

The definition of systemic/constitutional symptoms was relatively consistent across the fifteen articles that reported this clinical feature in the systematic review, with only three articles not providing a definition. Weight loss/anorexia, fever, asthenia, malaise, and fatigue were the symptoms most commonly included in the term systemic/constitutional symptoms by the articles that did give a definition. The most common combination of these were weight loss/anorexia, and either asthenia/fatigue/malaise. Fever was included in the definition in seven of the fifteen articles. A Read code for asthenia and malaise could not be found, but Read codes for fatigue were compiled. In the main analysis, fever, weight loss/anorexia, and fatigue were kept independent of each other. As a sensitivity analysis they were grouped under the heading constitutional symptoms. Three articles in the review defined constitutional symptoms using this definition.

Anxiety/depression, cancer, and diabetes are both common in the general population, with an estimated 10.2 per 100 people aged over 65 years having a recorded diagnosis of

anxiety/depression (Public Health England, 2017), and between 8 and 11 per 1000 person-years diagnosed with diabetes (Sharma, Nazareth, & Petersen, 2016). These conditions were not commonly reported in the articles included in the systematic review (4, 2, and 4 articles, respectively). However, due to their high prevalence in the population of interest (patients aged over 50 years) and lack of previous research into their association with a subsequent diagnosis of GCA, both were included in the case-control study.

Hypertension was defined by two different criteria. If a patient had a record of a hypertension Read code then they would be classified as having recorded hypertension. The second definition used prescription information. If a patient had a record of two or more hypertension medications prescribed on unique days during the periods of interest (as defined in Section 6.4.3 below) then they would be classified as having treated hypertension. This decision was taken because Read codes for chronic conditions, such as hypertension, may be added to a patient's record when initially diagnosed, and not used again thereafter, and may not specifically be consulted with routinely afterwards, particularly if well controlled. However, these patients will be treated with hypertensive medication (and coded as such) as it is a chronic condition. Therefore, to ensure all patients with hypertension were included in the analysis, prescription information was included in the definition of hypertension (Hippisley-Cox, Coupland, & Brindle, 2017).

Previous research has been conducted into the relationship between cancer and GCA (Miguel A. Gonzalez-Gay et al., 2007; Hill et al., 2010; Tanaz A Kermani et al., 2010; Stamatis et al., 2020), although the majority of published articles investigate the association with cancer after a diagnosis of GCA. The general consensus of these articles is that there is no increase in the risk of cancer for patients with GCA compared to the general population (Miguel A. Gonzalez-Gay et al., 2007; Hill et al., 2010; Stamatis et al., 2020). One study which

investigated cancer prior to a diagnosis of GCA (Tanaz A Kermani et al., 2010) found that there was a low prevalence of malignancy in patients prior to their diagnosis of GCA, and that there was no increase in the odds of GCA if there was a prior record of cancer. However, this study was set in the USA, and included a small sample of GCA patients which could have made the statistical analysis underpowered. In order to investigate if there is any increase in the odds of a GCA diagnosis with a prior history of malignancy in a UK population, cancer in any location will be included in this case-control study.

6.4.2.1 Time prior to GCA diagnosis

Research examining the clinical features that are indicative of a subsequent diagnosis of conditions like psychosis, schizophrenia, multiple sclerosis, rheumatoid arthritis, and Parkinson's disease have been published in recent years (Disanto et al., 2018; Mikanmaa et al., 2019; Muller et al., 2019; Postuma, 2019; Powers et al., 2020). The examined time-periods over which patients experience specified clinical features prior to the diagnosis of interest varies between conditions. For conditions with long latency periods, such as Parkinson's and multiple sclerosis, these time-periods are usually 5 years prior to diagnosis (Disanto et al., 2018; Marrie, 2019; Postuma, 2019). For other conditions, such as Type I diabetes, rheumatoid arthritis, and psychosis related conditions, this time period is most often 2 years prior to diagnosis, but can be 1 year prior to diagnosis (Addington et al., 2015; Muller et al., 2019; Townson, Cannings-John, Francis, Thayer, & Gregory, 2019). This period is often stratified into months; 1 month prior to diagnosis, 6 months prior, 12 or 18 months prior, and 24 months prior to diagnosis, with all time periods being cumulative (Addington et al., 2015; Muller et al., 2019). Based on these recent and previously published studies the

time-periods chosen for this study were ≤1 month prior, 6 months prior, 12 months prior, and 24 months prior to a diagnosis of GCA, with time periods being cumulative.

Symptoms, such as headache, visual impairment, and any non-chronic conditions were extracted from patients' records for the periods 24, 12, 6, and ≤1 months prior to the date of GCA diagnosis (Muller et al., 2019). Chronic conditions were extracted from records for the periods 24, 12, and 6 months prior to the date of GCA diagnosis. Due to the possibility that being diagnosed with any comorbidity ≤1 month prior to a GCA diagnosis could be due to misdiagnosis, this time-period was excluded from the comorbidity analysis. The results for symptoms and comorbidities are presented separately for ease of interpretability. Clinical features recorded on the same day as a diagnosis of GCA were included. All 14 clinical features were categorised into 'yes' or 'no', where yes was if a patient had 1 or more recorded consultations for that clinical feature, stratified by time period.

To investigate possible delay in diagnosis of GCA in primary care, the median time from first record of each clinical feature, at any point prior to GCA diagnosis, to the date of GCA diagnosis was calculated. This delay was initially examined just in the 24 months prior to a GCA diagnosis, and then across the entire time period from 1990-2017 to investigate if some clinical features were associated with a diagnosis of GCA before the 24 month period. The median is reported along with the interquartile range rather than the mean due to possible skewness of the data.

6.4.3 Covariates

The covariates to be used in the analysis for this study were BMI, smoking status, and alcohol consumption as indicators of a patients' general health status. Four articles included in the review in Chapter 3 recorded the prevalence of smoking in GCA patients prior to their

GCA diagnosis, with varying estimates. Few articles reported a patient's BMI, and no articles recorded information about patients' alcohol intake, hence there is little information about their relationship to GCA. In a sensitivity analysis, the Index of Multiple Deprivation (IMD 2015) was added to the analysis for patients in England who were registered at general practices consenting to linkage of their deprivation status, in order to check the robustness of the results to adjustment for deprivation.

BMI, smoking status, and alcohol consumption were taken as the last recorded value prior to the index date as these were more likely to reflect the patient's demographics at the time of GCA diagnosis. If this information was completely missing, i.e. they did not have a recorded value at any time, then the patient was classified as unrecorded for that variable. It could not be assumed that if the patient was missing the information for alcohol and smoking that they were a non-drinker or non-smoker, so they were allocated to the missing category. Code lists were compiled for BMI, smoking, and alcohol status (Appendix 6.1, Table 1). For BMI the Read/medcodes for height and weight were used along with the general code for BMI. BMI values were calculated from the height and weight recorded in the patient's record, if actual BMI was not recorded. Information on BMI, smoking, and alcohol consumption is found in the additional patient files (detailed in Chapter 4), which can be mapped to the clinical and referral files by the unique ID (patid) given to each patient. BMI was categorised into four categories; under/normal weight (<25kg/m^2), overweight (25-29.9kg/m^2), obese (≥30kg/m^2), and missing. These categories are based on the World Health Organisation's (WHO) recommended cut-offs (Weir & Jan, 2019). Where required, categories were merged to ensure they contained a similar number of patients. Smoking status was coded into four groups: current smoker, ex-smoker, non-smoker and missing. Alcohol consumption was categorised into five groups; non-drinker (0 units per week), light drinker

(1-7 units per week), moderate drinker (8-14 units per week), heavy drinker (≥15 units per week), and missing. These categorisations are based on a previous study using CPRD to investigate alcohol consumption in patients with rheumatoid arthritis who were taking methotrexate (Humphreys et al., 2017).

The IMD 2015 scores were categorised at quintile score by CPRD prior to data delivery, where 1 is the least deprived and 5 the most deprived compared to the rest of the population of England. Only patients registered at practices consenting to IMD 2015 linkage were included in the analysis.

6.4.4 Analysis

Patient characteristics were compared between cases and controls, and between the population from the main analysis, and the two sensitivity populations (described in section 6.4.4.1). The proportion of males and females, BMI category, smoking status, alcohol consumption, and where available, IMD 2015 score were calculated. In order to investigate the relationship between a diagnosis of GCA and prior recorded clinical features in primary care, conditional logistic regression was used to account for the matched sets of cases to controls with each clinical feature included in separate regression models.

Conditional logistic regression is implemented on matched data and conditioned on the matched pairs (Pearce, 2016). The response of conditional logistic regression is binary, in the case of this analysis an indicator variable that takes the value of 1, if the patient has GCA, and 0 if the patient does not have GCA. A matching variable linking each case to its controls must also be specified, otherwise the regression model will incorrectly assume that all observations are independent and will instead fit an unconditional logistic regression, which has been shown to give biased estimates when applied to matched data (Pearce, 2016).

If there are *s* matched sets and *p* independent variables, the formula used for conditional logistic regression is given by (3):

$$\mathrm{logit}(\mathrm{p}) = \alpha_1 + \alpha_2 \mathrm{z}_2 + \cdots + \alpha_\mathrm{s} \mathrm{z}_\mathrm{s} + \beta_1 \mathrm{x}_1 + \cdots + \beta_\mathrm{p} \mathrm{x}_\mathrm{p} \quad (3)$$

Where z_i are the binary indicators for each matched set, α_i are the regression coefficients associated with the matched set indicator variables, x_j are the covariates, and β_j are the regression coefficients to be estimated, where *i* is *1*:*s*, and *j* is *1*:*p*. Conditional logistic regression fits models to matched data based on maximum likelihood estimation.
Since the data was already matched on gender, year of birth, and general practice, they were not included as variables in the model. Unadjusted and adjusted analyses were conducted for each clinical feature under investigation. Models were adjusted for BMI, alcohol consumption, and smoking status.

6.4.4.1 Sensitivity analysis

Two sensitivity analyses were conducted on subsets of the data. Initially, as in Chapter 5, the definition of a GCA case was altered to include the requirement of one or more prescriptions of glucocorticoids within the first 6 months of a GCA diagnosis, alongside a Read code for GCA. A secondary sensitivity analysis was also conducted, further adjusting for deprivation data (as detailed in section 6.4.3) for patients with this linkage (all in England). For this subset of patients, models were adjusted for BMI, smoking status, alcohol consumption, and deprivation.

6.5 Results

6.5.1 Sample characteristics

A total sample size of 55,218 contained information on 9205 GCA cases matched with 46,013 controls. The mean age of cases was 72.6 years (SD = 10.3), and 71% were female; 32.5% were overweight and 20.6% were obese, 14.9% were current smokers, and 10.0% were moderate or heavy drinkers. The mean age of controls was also 72.6 years (SD = 10.3), 24.2% were overweight and 14.8% were obese, 9.9% were current smokers and 8.0% were moderate drinkers. Missing data on BMI, smoking status, and alcohol consumption was higher in controls than cases (Table 6.1).

After restriction of GCA cases to those who had a Read code and a prescription of glucocorticoids (sensitivity analysis 1), the remaining sample size was 49,455 (90% of the total data), with 8244 GCA cases and 41,211 controls (Table 6.1). Sample characteristics were similar to the GCA cases defined by a Read code without need for a prescription.

Restricting the sample to patients registered at practices in England with linkage to the IMD 2015 (sensitivity analysis 2) left 5240 GCA cases and 26,199 controls (Table 6.1). In total, 72 GCA cases (1.1%) in these practices did not have linkage to deprivation data, and 11.2% were from the most deprived area. 17.6% of cases were in the least deprived areas. Controls had a higher proportion of missing IMD 2015 linkage (3.9%). Similar to cases, the IMD quintile with the highest proportion of controls was the least deprived (17.5%), whilst the most deprived had the smallest proportion (9.9%).

Table 6.1: Patient demographics for cases and controls for main analysis and sensitivity analyses.

	Main analysis				Sensitivity analysis							
	Read code only[a]				Read code & prescription[b]				England only[c]			
	Cases (n = 9205)		Controls (n = 46013)		Cases (n = 8244)		Controls (n = 41211)		Cases (n = 5240)		Controls (n = 26199)	
	N	%	N	%	N	%	N	%	N	%	N	%
Mean age (SD)	72.6 (10.3)		72.6 (10.3)		72.9 (9.92)		72.9 (9.91)		72.6 (10.4)		72.5 (10.4)	
Median age (IQR)	74 (14)		74 (14)		74 (13)		74 (13)		74 (14)		74 (14)	
Female	6532	70.96	32659	70.98	5822	70.62	29410	71.36	3708	70.76	18540	70.77
Male	2673	29.04	13354	29.02	2362	28.65	11801	28.64	1532	29.24	7659	29.23
BMI												
Normal & underweight	3213	34.90	12548	27.27	2929	35.53	11328	27.49	1856	35.42	7248	27.67
Overweight	2989	32.47	11122	24.17	2703	32.79	10029	24.34	1703	32.50	6310	24.08
Obese	1898	20.62	6802	14.78	1664	20.18	6133	14.88	1029	19.64	3757	14.34
Missing	1105	12.00	15541	33.78	948	11.50	13721	33.29	652	12.44	8884	33.91
Smoking												
Current	1371	14.89	4554	9.90	1214	14.73	4071	9.88	738	14.08	2455	9.37
Non-smoker	2895	31.45	12174	26.46	2606	31.61	11046	26.80	1820	34.73	7734	29.52
Ex-smoker	2456	26.68	7437	16.16	2254	27.34	6804	16.51	1327	25.32	4073	15.55
Missing	2483	26.97	21848	47.48	2170	26.32	19290	46.81	1355	25.86	11937	45.56
Alcohol												
Never	1404	15.25	5881	12.78	1206	14.63	5206	12.63	583	11.13	2298	8.77
Light	3204	34.81	11750	25.54	2905	35.24	10642	25.82	1950	37.21	7441	28.40
Moderate	918	9.97	3683	8.00	835	10.13	3289	7.98	565	10.78	2248	8.58
Heavy	642	6.97	2670	5.80	561	6.80	2365	5.74	398	7.60	1647	6.29
Missing	3037	32.99	22029	47.88	2737	33.20	19709	47.82	1744	33.28	12565	47.96
IMD 2015												
Least deprived	-	-	-	-	-	-	-	-	1193	17.57	5951	17.53
2	-	-	-	-	-	-	-	-	1138	16.76	5529	16.29
3	-	-	-	-	-	-	-	-	1184	17.43	5731	16.88
4	-	-	-	-	-	-	-	-	892	13.14	4299	12.66
Most Deprived	-	-	-	-	-	-	-	-	761	11.21	3375	9.94
Missing	-	-	-	-	-	-	-	-	72	1.06	1314	3.87

a: Main analysis: GCA defined by Read code only

b: Sensitivity analysis 1: GCA defined using Read codes and glucocorticoid prescription; c: Sensitivity analysis 2: Patients registered at practices in England consenting to linkage with IMD 2015 only.

6.5.2 Associations of symptoms with GCA

In the main analysis, associations of symptoms were examined between cases and controls in the 24-month time-period prior to the index date of GCA diagnosis (Table 6.2 & Table 6.3). In the 24 months prior to index date, 43.2% of GCA cases had a record of a headache, 11.2% had a record of constitutional symptoms, and 32.4% had a record of elevated ESR. Only 2.0% of GCA cases had a record of jaw pain in the 24 months prior to index date, 0.6% had a record of fever, and 3.2% had a record of visual impairment in the same time-period. The proportions of GCA cases recording symptoms in the 24 months prior to index date was consistently higher than matched controls (Table 6.2).

Patients with GCA had consistently higher adjusted odds of experiencing all symptoms included in this analysis in the 24 months prior to index date than controls (Table 6.3). After adjustment for BMI, smoking status, and alcohol consumption GCA cases had; 56.26 (95% CI: 49.04, 64.56) times higher odds of a recorded elevated ESR than controls, and 3.07 (95% CI: 2.82, 3.36) times higher odds of recorded constitutional symptoms in the 24 months prior to index date. Despite low prevalence estimates, cases still had 12.55 (95% CI: 9.93, 15.87) and 4.06 (95% CI: 2.73, 6.04) times higher odds of visual impairment and fever, respectively, in the 24 months prior to index date.

Detailed results for headache, recorded elevated ESR, and fatigue will be presented in this section, due to the high prevalence and strong association between these and a subsequent diagnosis of GCA found in the systematic review in Chapter 3.

Table 6.2: Summary statistics for symptoms prior to a GCA diagnosis for cases (n = 9205) and controls (n = 46,103), stratified by time prior to diagnosis.

	24 months prior		**12 months prior**		**6 months prior**		**≤1 month prior**	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Headache								
No	5226 (56.77)	45203 (98.24)	5448 (59.19)	45577 (99.05)	5670 (61.60)	45779 (99.49)	6478 (70.37)	45961 (99.89)
Yes	3979 (43.23)	810 (1.76)	3757 (40.81)	436 (0.95)	3535 (38.40)	234 (0.51)	2727 (29.63)	52 (0.11)
Fever								
No	9150 (99.40)	45959 (99.88)	9162 (99.53)	45990 (99.95)	9174 (9.66)	46005 (99.98)	9183 (99.76)	-
Yes	55 (0.60)	54 (0.12)	43 (0.47)	23 (0.05)	31 (0.34)	8 (0.02)	22 (0.24)	-
Weight loss/Anorexia								
No	8952 (97.25)	45637 (99.18)	9029 (98.09)	45825 (99.59)	9075 (98.59)	45909 (99.77)	9151 (99.41)	46000 (99.97)
Yes	253 (2.75)	376 (0.82)	176 (1.91)	188 (0.41)	130 (1.41)	104 (0.23)	54 (0.59)	13 (0.03)
Visual impairment								
No	8911 (96.81)	45904 (99.76)	8957 (97.31)	45954 (99.87)	8997 (97.74)	45983 (99.93)	9067 (98.50)	46008 (99.99)
Yes	294 (3.19)	109 (0.24)	248 (2.69)	59 (0.13)	208 (2.26)	30 (0.07)	138 (1.50)	5 (0.01)
Fatigue								
No	8429 (91.57)	44924 (97.63)	8699 (94.50)	45402 (98.67)	8881 (96.48)	45681 (99.28)	9079 (98.63)	45939 (99.84)
Yes	776 (8.43)	1089 (2.37)	506 (5.50)	611 (1.33)	324 (3.52)	332 (0.72)	126 (1.37)	74 (0.16)
Recorded elevated ESR								
No	6219 (67.56)	45537 (98.77)	6378 (69.29)	45732 (99.20)	6547 (71.12)	45845 (99.44)	7179 (77.99)	45969 (99.90)
Yes	2986 (32.44)	476 (1.23)	2827 (30.71)	281 (0.80)	2658 (28.88)	168 (0.66)	2026 (22.01)	44 (0.10)
Arthralgia/Myalgia								
No	8531 (92.68)	45358 (98.58)	8770 (95.27)	45650 (99.21)	8917 (96.87)	45821 (99.58)	9120 (99.08)	45977 (99.92)
Yes	674 (7.32)	655 (1.42)	435 (4.73)	363 (0.79)	288 (3.13)	192 (0.42)	85 (0.92)	36 (0.08)
Jaw pain								
No	9022 (98.01)	45979 (99.93)	9039 (98.20)	45997 (99.97)	9055 (98.37)	46001 (99.97)	9105 (98.91)	-
Yes	183 (1.99)	34 (0.07)	166 (1.80)	16 (0.03)	150 (1.63)	12 (0.03)	100 (1.09)	-
Constitutional symptoms								
No	8178 (88.84)	44538 (96.79)	8602 (93.45)	45293 (98.44)	8798 (95.58)	45620 (99.15)	9129 (99.17)	45999 (99.97)
Yes	1027 (11.16)	1475 (3.21)	603 (6.55)	720 (1.56)	407 (4.42)	393 (0.85)	76 (0.83)	14 (0.03)

Missing cells (-) indicate less than 5 events for that outcome, therefore CPRD does not permit reporting for those outcomes.

Table 6.3: Results of conditional logistic regression by symptom, showing odds ratio and 95% confidence intervals stratified by time period prior to date of GCA diagnosis. Missing cells (-) indicate less than 5 events for that outcome, therefore CPRD does not permit reporting for those outcomes.

	24 months prior		**12 months prior**		**6 months prior**		**≤1 month prior**	
	Unadjusted	Adjusted[†]	Unadjusted	Adjusted[†]	Unadjusted	Adjusted[†]	Unadjusted	Adjusted[†]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Headache								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Yes	49.80 (44.79, 55.38)	44.31 (36.77, 49.37)	84.01 (73.24, 96.37)	76.61 (66.64, 88.06)	145.70 (121.40, 174.90)	134.81 (112.08, 162.16)	424.20 (299.40, 601.10)	402.17 (283.40, 570.72)
Fever								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	5.15 (3.53, 7.51)	4.06 (2.73, 6.04)	9.35 (5.63, 15.51)	7.60 (4.45, 12.99)	19.37 (8.91, 42.15)	17.90 (7.90, 40.58)	110.00 (14.83, 816.10)	99.72 (13.17, 755.11)
Weight loss/Anorexia								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	3.44 (2.92, 4.04)	2.71 (2.30, 3.21)	4.71 (3.83, 5.79)	3.78 (3.05, 4.68)	6.29 (4.86, 8.15)	5.14 (3.93, 6.73)	20.77 (11.34, 38.05)	16.59 (8.90, 30.93)
Visual impairment								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	14.11 (11.27, 17.67)	12.55 (9.93, 15.87)	21.99 (16.45, 29.39)	20.77 (15.38, 28.06)	35.73 (24.23, 52.70)	35.00 (23.46, 52.24)	171.80 (63.56, 464.20)	172.17 (63.18, 469.15)
Fatigue								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	3.94 (3.57, 4.34)	3.12 (2.82, 3.45)	4.45 (3.93, 5.03)	3.56 (3.14, 4.05)	5.16 (4.41, 6.04)	4.19 (3.56, 4.93)	8.60 (6.44, 11.47)	7.13 (5.29, 9.60)
Recorded elevated ESR								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	62.70 (54.78, 71.77)	56.26 (49.04, 64.56)	96.03 (81.17, 113.60)	87.75 (74.00, 104.05)	128.40 (105.30, 156.40)	118.78 (97.24, 145.09)	288.60 (206.60, 403.10)	272.85 (194.96, 381.87)
Arthralgia/ Myalgia								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	5.70 (5.09, 6.39)	4.60 (4.09, 5.18)	6.34 (5.50, 7.32)	5.17 (4.46, 6.00)	7.72 (6.42, 9.29)	6.33 (5.22, 7.47)	12.07 (8.14, 17.89)	10.10 6.74, 15.15)
Jaw Pain								
No	Ref	Ref	Ref	Ref	Ref	Ref	-	-
Yes	26.91 (18.66, 38.81)	22.29 (15.28, 32.50)	51.87 (31.06, 86.65)	45.59 (27.00, 77.00)	62.50 (34.72, 112.50)	56.08 (30.78, 102.20)	-	-

Constitutional symptoms††								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	3.89 (3.57, 4.23)	3.07 (2.82, 3.36)	4.44 (3.97, 4.96)	3.55 (3.16, 3.99)	5.40 (4.69, 6.22)	4.42 (3.81, 5.12)	27.14 (15.35, 48.00)	22.32 (12.43, 40.10)

† Adjusted for BMI, smoking status, and alcohol consumption. * Too few events to report jaw pain results. †† Defined as' fever, weight loss/anorexia, and fatigue

6.5.2.1 Headache

In the 24 months prior to a diagnosis of GCA, 43.2% of cases had a recorded consultation for a headache compared to 1.76% of controls (Table 6.4). 40.8% of cases in the 12 months prior had a recorded consultation for headache, compared to 1.0% of controls. 29.6% of cases had a recorded headache in the month prior to a diagnosis of GCA, compared to 0.1% of controls. GCA cases had 44.31 (95% CI: 36.77, 49.37) times higher odds of reporting a headache in the 24 months prior to index date than controls after adjustment. This increased to a 402.17 (95% CI: 283.40, 570.72) times greater odds of reporting a headache in the 1 month prior to the index date than controls.

Table 6.4: Association between time of headache consultation and subsequent diagnosis of GCA.

			Conditional logistic regression	
Time prior to GCA diagnosis	**Cases N (%)**	**Controls N (%)**	**Unadjusted OR (95% CI)**	**Adjusted[†] OR (95% CI)**
24 months	3979 (43.23)	810 (1.76)	49.80 (44.79, 55.38)	44.31 (36.77, 49.37)
12 months	3757 (40.81)	436 (0.95)	84.01 (73.24, 96.37)	76.61 (66.64, 88.06)
6 months	3535 (38.40)	234 (0.51)	145.70 (121.40, 174.90)	134.81 (112.08, 162.16)
≤1 month	2727 (29.63)	52 (0.11)	424.20 (299.40, 601.10)	402.17 (283.40, 570.72)

† Adjusted for BMI, alcohol consumption, and smoking status.

6.5.2.2 Recorded elevated ESR

In the 24 months prior to index date 32.4% and 1.2% of cases and controls had recorded elevated ESR, respectively (Table 6.5). In the 12 months prior to index date 30.7% of cases, and 0.8% of controls had a record of elevated ESR; in the 6 months prior 28.9% and 0.7%, and ≤1 month prior 22.0% and 0.1%, respectively. GCA cases had 56.26 (95% CI: 49.04, 64.56) times higher odds of having a recorded elevated ESR in the 24 months prior to their

index date than controls after adjustment. The strength of association of recorded elevated ESR with GCA continued to increase at each time point closer to GCA diagnosis.

Table 6.5: Association between time of recorded elevated ESR consultation and subsequent diagnosis of GCA

			Conditional logistic regression	
Time prior to GCA diagnosis	**Cases N (%)**	**Controls N (%)**	**Unadjusted OR (95% CI)**	**Adjusted† OR (95% CI)**
24 months	2986 (32.44)	476 (1.23)	62.70 (54.78, 71.77)	56.26 (49.04, 64.56)
12 months	2827 (30.71)	281 (0.80)	96.03 (81.17, 113.60)	87.75 (74.00, 104.05)
6 months	2658 (28.88)	168 (0.66)	128.40 (105.30, 156.40)	118.78 (97.24, 145.09)
≤1 month	2026 (22.01)	44 (0.10)	288.60 (206.60, 403.10)	272.85 (194.96, 381.87)

† Adjusted for BMI, alcohol consumption, and smoking status.

6.5.2.3 Fatigue

In the 24 months prior to a diagnosis of GCA

8.4% of cases had a record of fatigue compared to 2.4% of controls (Table 6.6). GCA cases had 3.12 (95% CI: 2.82, 3.45) times higher odds of reporting fatigue in the 24 months prior to index date than controls after adjustment. The increased odds of reporting fatigue increased at each subsequent time point prior to GCA diagnosis.

Table 6.6: Association between time of fatigue consultation and subsequent diagnosis of GCA

			Conditional logistic regression	
Time prior to GCA diagnosis	**Cases N (%)**	**Controls N (%)**	**Unadjusted OR (95% CI)**	**Adjusted† OR (95% CI)**
24 months	776 (8.43)	1089 (2.37)	3.94 (3.57, 4.34)	3.12 (2.82, 3.45)
12 months	506 (5.50)	611 (1.33)	4.45 (3.93, 5.03)	3.56 (3.14, 4.05)
6 months	324 (3.52)	332 (0.72)	5.16 (4.41, 6.04)	4.19 (3.56, 4.93)
≤1 month	126 (1.37)	74 (0.16)	8.60 (6.44, 11.47)	7.13 (5.29, 9.60)

† Adjusted for BMI, alcohol consumption, and smoking status.

6.5.2.4 Time from first recorded symptom to GCA diagnosis

Time between the first record of each symptom and the date of GCA diagnosis varied across symptoms (Table 6.7). Each symptom had large variation, shown by the large values of the IQR, implying that this data was highly skewed.

Table 6.7: Median time between first record of each symptom and a diagnosis of GCA in the 24 months prior to GCA diagnosis, and all time (1990-2017).

Clinical feature	**Median number of days (IQR) in the 24 months prior to GCA diagnosis**	**Median number of days (IQR) all time (1990-2017)**
Headache	25 (121)	255 (2385)
Jaw pain	26 (86)	173 (1289.5)
Visual impairment	48 (253)	657.5 (2384.8)
Recorded elevated ESR	76 (339)	1879 (4003)
Fever	113 (300)	1816 (3836.75)
Weight loss/anorexia	200 (426)	1317.5 (2881.8)
Arthralgia/myalgia	286 (412)	1969 (3251.8)
Fatigue	300 (415)	2043 (2945.3)

The symptom with the shortest time from first recorded onset to GCA diagnosis, in the 24 months prior to index date, was headache, with a median of 25 days (IQR: 121 days). This implies that a headache is first reported less than a month prior to a GCA diagnosis. The symptom with the second shortest time was jaw pain, with a median of 26 days (IQR: 86 days). Visual impairment had a median time from recorded onset to GCA diagnosis of 48 days (IQR: 253 days), which approximately equates to 1 ½ months. The symptom with the longest time between first recorded onset and GCA diagnosis was fatigue, with a median of 300 days (IQR: 415), which equates to just under a year from first recorded onset to eventual GCA diagnosis.

The symptom with the shortest time from first recorded onset to GCA diagnosis, across the entire time-period (1990-2017), was jaw pain, with a median of 173 days (IQR: 1290 days).

This approximately equates to between 5/6 months between the first recorded onset of jaw pain and an eventual diagnosis of GCA. The symptom with the second shortest time was headache with a median of 255 days (IQR: 2385 days), or 8/9 months. Visual impairment had a median time from first recorded onset of 658 days (IQR: 2385 days), or 22 months. The symptom with the longest time was fatigue, with a media
n of 2043 days (IQR: 2945 days), or 5/6 years.

6.5.3 Associations of comorbidities with GCA

Associations of comorbid features were examined between cases and controls in the 6, 12, and 24 months prior to their index date (Table 6.8,
Table 6.9). In the 24 months prior to index date, 12.6% of GCA cases had a record of cardiovascular/cerebrovascular conditions; 7.8% had a record of anxiety/depression; and 4.2% had a record of cancer. The proportions of GCA cases with recorded comorbidities in the 24 months prior to index date was consistently higher than matched controls (Table 6.8). GCA cases had consistently higher odds of all comorbidities included in this analysis recorded in the 24 months prior to index date than controls (
Table 6.9). After adjustment for BMI, smoking status, and alcohol consumption, GCA cases had 2.03 (95% CI: 1.88, 2.20) times higher odds of cardiovascular/cerebrovascular conditions than controls; 2.19 (95% CI: 1.99, 2.42) times higher odds of anxiety/depression, and 1.34 (95% CI: 1.19, 1.52) times higher odds of cancer in the 24 months prior to index date. The results for hypertension, diabetes, and PMR will be presented in more detail in this section.

Table 6.8: Summary statistics for comorbidities prior to a GCA diagnosis for cases (n = 9205) and controls (n = 46,103), stratified by time prior to diagnosis.

	24 months prior		**12 months prior**		**6 months prior**	
	Cases	Controls	Cases	Controls	Cases	Controls
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Treated hypertension						
No	3846 (41.78)	32485 (70.60)	4068 (44.19)	33964 (73.81)	4239 (46.05)	34644 (75.29)
Yes	5359 (58.21)	13168 (28.62)	5137 (55.81)	12049 (26.19)	4966 (53.95)	11369 (24.71)
Recorded hypertension						
No	8169 (88.75)	43320 (94.15)	8554 (92.93)	44465 (96.64)	8799 (95.59)	45146 (98.12)
Yes	1036 (11.25)	2693 (5.85)	651 (7.07)	1548 (3.36)	406 (4.41)	867 (1.88)
Cardiovascular/ Cerebrovascular						
No	8043 (87.38)	43452 (94.43)	8427 (91.55)	44546 (96.81)	8724 (94.77)	45196 (98.22)
Yes	1162 (12.62)	2561 (5.57)	778 (8.45)	778 (3.19)	481 (5.23)	817 (1.78)
Anxiety/ Depression						
No	8488 (92.21)	44559 (96.84)	8761 (95.18)	45192 (98.22)	8921 (96.91)	45570 (99.04)
Yes	717 (7.79)	1454 (3.16)	444 (4.82)	821 (1.78)	284 (3.09)	443 (0.96)
PMR						
No	8097 (87.96)	45815 (99.57)	8274 (89.89)	45887 (99.73)	8421 (91.48)	45927 (99.81)
Yes	1108 (12.04)	198 (0.43)	931 (10.11)	126 (0.27)	784 (8.52)	86 (0.19)
Diabetes						
No	8240 (89.52)	43660 (94.89)	8367 (90.90)	44136 (95.92)	8607 (93.50)	44783 (97.33)
Yes	965 (10.48)	2353 (5.11)	838 (9.10)	1877 (4.08)	598 (6.50)	1230 (2.67)
Cancer						
No	8821 (95.83)	44779 (97.32)	8972 (97.47)	45343 (98.54)	9069 (98.52)	45667 (99.25)
Yes	384 (4.17)	1234 (2.68)	233 (2.53)	670 (1.46)	136 (1.48)	346 (0.75)

Table 6.9: Results from the conditional logistic regression for comorbidities, showing odds ratios and 95% confidence intervals, stratified by time prior to index date.

	24 months prior		12 months prior		6 months prior	
	Unadjusted	Adjusted†	Unadjusted	Adjusted†	Unadjusted	Adjusted†
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Recorded hypertension						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	2.16 (1.99, 2.33)	1.67 (1.54, 1.82)	2.32 (2.10, 2.56)	1.80 (1.62, 1.99)	2.52 (2.22, 2.85)	1.94 (1.71, 2.21)
Treated Hypertension						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	3.80 (3.62, 3.99)	2.78 (2.64, 2.93)	3.87 (3.69, 4.07)	2.86 (2.72, 3.02)	3.86 (3.68, 5.06)	2.87 (2.73, 3.02)
Cardiovascular/ Cerebrovascular						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	2.52 (2.34, 2.72)	2.028 (1.88, 2.20)	2.88 (2.63, 3.16)	2.32 (2.11, 2.56)	3.12 (2.77, 3.50)	2.50 (2.21, 2.83)
Anxiety/ Depression						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	2.67 (2.43, 2.93)	2.19 (1.99, 2.42)	2.86 (2.54, 3.23)	2.38 (2.10, 2.69)	3.33 (2.86, 3.88)	2.83 (2.41, 3.32)
PMR						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	33.39 (28.33, 39.36)	30.27 (25.56, 35.84)	41.92 (34.40, 51.08)	38.08 (31.11, 46.60)	52.53 (41.39, 66.67)	48.63 (38.18, 62.00)
Diabetes						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	2.21 (2.04, 2.40)	1.58 (1.46, 1.72)	2.40 (2.21, 2.62)	1.72 (1.57, 1.88)	2.58 (2.33, 2.85)	1.85 (1.66, 2.05)
Cancer						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.58 (1.41, 1.78)	1.34 (1.19, 1.52)	1.76 (1.52, 2.05)	1.50 (1.28, 1.76)	1.98 (1.62, 2.42)	1.68 (1.36, 2.06)

† Adjusted for BMI, smoking status, and alcohol consumption

6.5.3.1 Hypertension

There was a difference in the prevalence of hypertension between the two definitions used (Table 6.10). 11.3% of cases had recorded hypertension in the 24 months prior to index date, in contrast to 58.2% who had treated hypertension in the same time-period. There was a difference between controls in the 24 months prior to index date, with 5.9% having recorded and 28.6% having treated hypertension.

Table 6.10: Association between time of first recorded hypertension and subsequent diagnosis of GCA

			Conditional logistic regression	
	Cases N (%)	**Controls N (%)**	**Unadjusted OR (95% CI)**	**Adjusted† OR (95% CI)**
Recorded				
24 months	1036 (11.25)	2693 (5.85)	2.16 (1.99, 2.33)	1.67 (1.54, 1.82)
12 months	651 (7.07)	1548 (3.36)	2.32 (2.10, 2.56)	1.80 (1.62, 1.99)
6 months	406 (4.41)	867 (1.88)	2.52 (2.22, 2.85)	1.94 (1.71, 2.21)
Treated				
24 months	5359 (58.21)	13168 (28.62)	3.80 (3.62, 3.99)	2.78 (2.64, 2.93)
12 months	51375 (55.81)	12049 (26.19)	3.87 (3.69, 4.07)	2.86 (2.72, 3.02)
6 months	4966 (53.95)	11369 (24.71)	3.86 (3.68, 5.06)	2.87 (2.73, 3.02)

† Adjusted for BMI, alcohol consumption, and smoking status.

In the conditional logistic regression, cases had higher odds of hypertension, both recorded and treated at every time point prior to index date. The odds ratios were larger for treated, than recorded hypertension. Cases had 2.78 (95% CI: 2.64, 2.93) times higher odds of treated hypertension after adjustment in the 24 months prior to index date (Table 6.10). This contrasted to the 1.67 (95% CI: 1.54, 1.82) times higher odds for cases having a recorded hypertension Read code in the same time-period. Odds of recorded hypertension increased the closer to the index date it was recorded. However, the odds of treated hypertension remained stable over the same time-period.

6.5.3.2 Diabetes

In the 24 months prior to index date, 10.5% of cases had a recorded diagnosis of diabetes, compared to 5.1% of controls (Table 6.11). After adjustment, cases had 1.58 (95% CI: 1.46, 1.72) times higher odds of a recorded diagnosis of diabetes in the 24 months prior to index date than controls. There was consistently more cases with a recorded diagnosis of diabetes than controls at every time point prior to index date. Cases had consistently significant higher odds of diabetes prior to index date than controls.

Table 6.11: Association between time of diabetes consultation and subsequent diagnosis of GCA

			Conditional logistic regression	
	Cases (%)	**Controls (%)**	**Unadjusted OR (95% CI)**	**Adjusted† OR (95% CI)**
24 months	965(10.48)	2353 (5.11)	2.21 (2.04, 2.40)	1.58 (1.46, 1.72)
12 months	838 (9.10)	1877 (4.08)	2.40 (2.21, 2.62)	1.72 (1.57, 1.88)
6 months	598 (6.50)	1230 (2.67)	2.58 (2.33, 2.85)	1.85 (1.66, 2.05)

† Adjusted for BMI, alcohol consumption, and smoking status.

6.5.3.3 PMR

In the 24 months prior to index date, 12.0% of GCA cases had a recorded diagnosis of PMR, compared to 0.4% of controls (Table 6.12). After adjustment, GCA cases had 30.27 (95% CI: 25.56, 35.84) times higher odds of a PMR diagnosis in the 24 months prior to index date than controls. At each time point prior to index date there was consistently higher proportion of GCA cases with a record of PMR than controls, and significantly higher odds of a PMR diagnosis prior to index date.

Table 6.12: Association between time of PMR consultation and subsequent diagnosis of GCA

			Conditional logistic regression	
	Cases (%)	**Controls (%)**	**Unadjusted OR (95% CI)**	**Adjusted† OR (95% CI)**
24 months	1108 (12.04)	198 (0.43)	33.39 (28.33, 39.36)	30.27 (25.56, 35.84)
12 months	931 (10.11)	126 (0.27)	41.92 (34.40, 51.08)	38.08 (31.11, 46.60)
6 months	784 (8.52)	86 (0.19)	52.53 (41.39, 66.67)	48.63 (38.18, 62.00)

† Adjusted for BMI, alcohol consumption, and smoking status.

6.5.3.4 Time from first recorded comorbidity to GCA diagnosis

Time from first recorded comorbidity to GCA diagnosis varied between comorbidities (Table 6.13). However, time from first recorded comorbidity onset and diagnosis of GCA varied between patients, evident by the large IQR values.

Table 6.13: Median time between first record of each comorbidity and a diagnosis of GCA,

Clinical feature	**Median number of days (IQR) in the 24 months prior to GCA diagnosis**	**Median number of days (IQR) all time (1990-2017)**
PMR	215 (439)	480 (1388)
Cancer	343 (392)	2462 (3689)
Cardiovascular/Cerebrovascular	371 (425)	2551 (3704.5)
Anxiety/depression	398 (411)	3875 (5075.5)
Recorded Hypertension	404 (421)	3228 (3832)
Diabetes	452 (360)	1742 (2676)

The comorbidity with the shortest time from first record, within 24 months prior to the date of GCA diagnosis, was PMR, with a median of 215 days (IQR: 439 days), approximately 7 months. Cancer had the second shortest time from first record, with a median of 343 days (IQR: 392), or just under a year. The comorbidity with the longest time from first record, within 24 months prior to GCA diagnosis, was diabetes with a median of 452 days (IQR: 360), or 15 months.

The comorbidity with the shortest time from first ever record, during the entire time period from 1990-2017, was PMR, with a median of 480 days (IQR: 1388 days), approximately a year and a quarter, between first onset and a diagnosis of GCA. Diabetes had the second shortest period between first record and GCA diagnosis, with a median of 1742 days (IQR: 2676), approximately four and three-quarter years. The comorbidity with the longest period between first onset and GCA diagnosis was anxiety/depression, with 3875 days (IQR: 5076), approximately ten and a half years.

6.5.4 Sensitivity analyses

The definition of a GCA case was altered for the first sensitivity analysis by including glucocorticoid prescription information. The definition of a GCA case in this sensitivity analysis has been described in section 6.4.4.1. After this condition was applied there were 8244 GCA cases eligible to be included in the analysis, with 41,211 matched controls. Results from the prescription sensitivity analysis were similar to the results of the Read code only definition of GCA (Appendix 6.1, Tables 2 & 3).

The second sensitivity analysis conducted on the data limited the number of cases to those who had an IMD 2015 value. The eligibility for cases and controls to be included in this analysis is given in section 6.4.4.1. In this sensitivity analysis there were 5240 GCA cases and 26,199 matched controls. The results from this sensitivity analysis were similar to the main analysis, and the previous prescription sensitivity analysis.

6.6 Discussion

6.6.1.1 Overview

In this case-control study examining the prevalence and association of clinical features present in primary care prior to GCA diagnosis, patients with GCA had increased odds of presenting with all 14 clinical features in the 24 months prior to their diagnosis of GCA than matched controls. Despite this association, the prevalence of some clinical features (fever, fatigue, jaw pain, weight loss/anorexia, and visual impairment) was low in this study in the 24 months prior to GCA diagnosis. Clinical features that were highly prevalent were headache, recorded elevated ESR, and treated hypertension. Patients who have a diagnosis of GCA have increased odds of a headache, recorded elevated ESR, weight loss/anorexia, fatigue, visual impairment, arthralgia/myalgia, jaw pain, hypertension, diabetes, cardiovascular/cerebrovascular diseases, anxiety/depression, cancer, and PMR in the 24 months prior to their diagnosis of GCA. These associations reached statistical significance, and maintained after adjustment for BMI, alcohol, and smoking consumption.

6.6.1.2 Time to diagnosis

Four time points prior to GCA diagnosis were examined in this study; 24 months, 12 months, 6 months, and ≤1 month prior. Symptoms had stronger associations with a GCA diagnosis than comorbidities, evident by the larger odds ratios observed for symptoms. The strength of association of all symptoms increased the closer they were recorded to the date of GCA diagnosis. This pattern was not the same for comorbidities, whose association with a GCA diagnosis remained stable at 24 and 12 months prior to diagnosis, with a small increase at 6 months, possibly due to surveillance bias as this was the median time for the first onset of symptoms prior to a GCA diagnosis.

The time between first recorded onset and a GCA diagnosis varied across clinical features. The median time from recorded onset to GCA diagnosis was smaller for symptoms than comorbidities. In the 24 months prior to a GCA diagnosis, the symptoms with the shortest median time from first recorded onset to GCA diagnosis were headache and jaw pain, both at just under a month before the date of GCA diagnosis. Symptoms such as fever, and weight loss/anorexia had the longest time from first recorded onset to GCA diagnosis. This implies that GPs are more likely to consider GCA as a diagnosis when patients present with jaw pain and/or a headache, in contrast to the remaining symptoms investigated in this study. It is of concern that the delay between first recorded onset of visual impairment and eventual GCA diagnosis was almost 2 months, considering visual impairment is a medical emergency.

The median time from first recorded onset to GCA diagnosis was longer for comorbidities. The comorbidity with the shortest median time from first recorded onset was PMR, at approximately 6/7 months. This difference in median time from first recorded onset to GCA diagnosis could imply a difference in the relationship between symptoms and comorbidities with a GCA diagnosis. Where symptoms could be indicating factors for a GCA diagnosis, comorbidities, due to their increased time from first onset to GCA diagnosis, could be viewed as risk factors. Hence, an indicator would present itself when the patient's GCA has already developed, but a risk factor would increase the risk of a subsequent diagnosis of GCA, but not necessarily that GCA would develop.

The source of this time from first recorded onset of clinical features to GCA diagnosis is a best estimate, as it is impossible to quantify this exactly in the current study. It is not possible in studies using EHR to quantify the time from actual first clinical feature onset to the time it was first recorded in their patient file. For symptoms like headache and jaw pain, patients may self-medicate rather than visit a GP, or with respect to jaw pain may initially

visit a dentist, thereby lengthening the time from symptom onset to symptom recording. The second source of this delay between symptom recording and diagnosis is the delay between a referral to a specialist to confirm diagnosis and when the diagnosis is recorded in the patient's primary care record, and from the date of referral to the date of the appointment with a specialist. Further work should try and investigate the true source of delay between first recorded symptom onset and a GCA diagnosis. It should be noted that NICE guidelines recommend that patients suspected of having GCA should be immediately treated with glucocorticoids without waiting for confirmation of diagnosis (NICE CKS, 2020). Therefore, it is possible that despite delays in diagnosis, some patients are still treated to prevent future visual loss.

6.6.1.3 Symptoms

Headache, found in this analysis to be prevalent (43%) prior to a diagnosis of GCA, was smaller than the prevalence estimate (77%) produced in the meta-analysis of the review in Chapter 3. Articles included in the review were mainly conducted in secondary care, therefore this difference could be due to a difference in the way of recording between the two healthcare settings. It is also possible that the prevalence estimate in this analysis reflects the proportion of patients who mainly, or only, present with a headache prior to their GCA diagnosis, and may have missed patients who present with headache along with a range of other symptoms that are simply not recorded, or recorded in the free text section of a patient's record that was not available for this analysis. The analysis in this chapter found headache to be highly associated with a diagnosis of GCA in the two years prior to GCA diagnosis. The result produced in the review showed less than 2 times higher odds, compared to the 44 times higher odds of this analysis.

In conjunction with headache, the review found that elevated ESR and visual impairment were associated with a diagnosis of GCA. The pooled prevalence of elevated ESR in the review was 76%, compared to the 32% in this analysis. Both the review and this study found a strong association between elevated ESR and a diagnosis of GCA, with the association stronger in this study. Regardless of possible differences, both the review and this study conclude that recorded elevated ESR is associated with a GCA diagnosis. Currently, NICE guidelines suggest that ESR should be measured in patients with suspected GCA, but may not always be tested in preference of other inflammatory markers i.e. c-reactive protein or plasma viscosity, the results from blood tests regarding specific measures like ESR are simply not formally coded individually into a patient's record or entered as free text.

The previously reported prevalence of visual loss in GCA patients prior to their diagnosis is 20% (NICE CKS, 2020). The review found the prevalence of visual impairment, which included loss and other impairments such as diplopia, to be 44%. This study found the prevalence of visual impairment to be 3%. This disparity may be due to lack of recording of symptoms via Read codes in primary care. As explained in section 6.6.1.2, not all symptoms may be recorded via Read code during a consultation and may instead be added into the free text section, not available in this analysis. The current NICE guidelines instruct GPs to immediately give patients with visual impairment a prescription of glucocorticoids, due to suspected GCA and to prevent permanent vision loss (NICE CKS, 2020). This may result in only the prescription being coded, and not the visual symptoms.

Fatigue, along with weight loss/anorexia and fever, was considered to come under the term "constitutional/systemic symptoms" highlighted in the systematic review. The articles included in the review did not always make it clear how many, or in what combination, these symptoms were presented with. In this study all three were kept independent of one

another to investigate their individual associations with a subsequent diagnosis of GCA, and subsequently incorporated to investigate their joint association with a diagnosis of GCA. Recording of all three were highly associated with a diagnosis of GCA. GCA cases presenting with fever had higher increased odds of a subsequent GCA diagnosis than those presenting with weight loss/anorexia, although both were significantly associated with a diagnosis of GCA. Including all three under the heading of constitutional symptoms maintained this significant association with a diagnosis of GCA. After comparison with the results of the systematic review, constitutional/systemic symptoms did not have a significant association with a positive temporal artery biopsy in the review. Overall, there is little benefit of combining fever, fatigue, weight loss, and anorexia under one term. Any usefulness such a term would bring to research and primary care recording is inhibited by the lack of consistency in the term's definition regarding symptoms included, and what combination, if any, they are presented in. An area for future research would be to develop an official definition of constitutional symptoms and what symptom requirements are needed for it to be used in a patient's record.

The systematic review conducted in Chapter 3 found that jaw claudication, defined as pain in the jaw whilst eating, was associated with a diagnosis of GCA. There is currently no corresponding Read code for jaw claudication. There are codes for general and limb specific claudication, pain whilst chewing, amongst other related forms of claudication, but none were suitable to represent jaw claudication. SNOMED clinical terms (SNOMED CT) is a medical coding system developed in the UK which is set to replace Read codes. As of April 2018, the NHS began to phase SNOMED codes in to replace the currently used Read codes. Eventually this will lead to Read codes becoming obsolete within UK general practice. There is a SNOMED code for jaw claudication, and an area of future work in the research of GCA in

primary care should be to conduct a study using SNOMED codes, thereby allowing the inclusion of jaw claudication as a specific clinical feature, conditional on appropriate and correct usage by GPs. However, it will not be available in historic data, prior to the introduction of SNOMED codes. The closest Read code available was jaw pain, which was used in this study, but does not exactly match the definition of jaw claudication.

6.6.1.4 Comorbidities

Patients who have a record of hypertension or PMR in the two years prior to their date of GCA diagnosis have higher odds of a diagnosis of GCA than controls. Other comorbidities that had a significant, but weaker, association with a diagnosis of GCA were; cardiovascular/cerebrovascular conditions, diabetes, cancer, and anxiety/depression. The articles included in the systematic review mainly reported findings on symptoms, hence results on the relationship between comorbidities and a diagnosis of GCA were sparse. This study has found that some comorbidities, like hypertension, may be risk factors for GCA. PMR was the only comorbidity frequently reported in review articles, this is likely due to its known association with GCA. The review found that PMR occurred in a third (34%) of patients prior to a positive temporal artery biopsy. However, the moderate positive association between PMR and a positive temporal artery biopsy was not statistically significant. Findings from this study suggest that the prevalence of PMR prior to a GCA diagnosis is lower (12%). However, PMR was found to be strongly associated with a subsequent diagnosis of GCA in this study. The difference between the results of this study and the review may be due to the differences in comorbidity recording between primary and secondary care. PMR can also be difficult to diagnose since there is no diagnostic test

available for this condition (G. Nesher & Breuer, 2016), hence PMR may not be diagnosed, or coded into a patient's primary care record.

Hypertension was found to be one of the most prevalent comorbidities in this study, with 50% of cases having a record of hypertensive medication in the 24 months prior to their GCA diagnosis. Hypertension was also found to be strongly associated with a GCA diagnosis in this study. In comparison, hypertension was not frequently reported in the articles included in the review and had a moderate/low prevalence (31%).

Hypertension, for the purposes of this study, was defined two ways; recorded and treated. Treated hypertension was found to be more prevalent in both case and control populations when compared to recorded. However, both were significantly associated with a subsequent diagnosis of GCA. This indicates that when researching hypertension using primary care EHR, treated hypertension should be used to ensure patients with hypertension are not missed, rather than relying solely on Read codes, which in this study produced low consultation prevalence estimates. Previous studies have found that adverse effects of long-term glucocorticoid use, such as that used to treat GCA, is the development of hypertension (Ness, Bley, Schmidt, & Lamprecht, 2013). However, this is usually after a diagnosis of GCA, whereas this work has identified the presence of hypertension before the GCA diagnosis. This could imply there is an association between pre-existing hypertension and a subsequent diagnosis of GCA, or that hypertension may cause GCA. However, investigation of this possible association is an area for future work.

Cancer was not significantly associated with a diagnosis of GCA at all time periods prior. A previous case-control study investigating the association between a prior diagnosis of cancer and a subsequent diagnosis of GCA in the USA found that GCA patients had a lower risk of prevalent cancer prior to their diagnosis of GCA (Tanaz A Kermani et al., 2010). However,

when cancer was investigated 12 months prior to a GCA diagnosis, the OR was 1.25 after adjustment for age, sex, and year of GCA diagnosis, but was not statistically significant. This result is very similar to the odds ratio found in this study for cancer 12 months prior to diagnosis (OR = 1.50), which was statistically significant. The study by Kermani et al (2010) had a small sample size of only 207 GCA patients, and matched cases to controls on a ratio of 1:2. Therefore it is possible that the analysis conducted in that study was underpowered. The results from this study, which is unlikely to be underpowered, found that there was an association between cancer and GCA.

6.1.1.1 Comparison to the systematic review

Overall, the prevalence estimates found in the systematic review were larger than those produced in this study. However, both agreed that headache, elevated ESR, and constitutional symptoms were the symptoms with the largest prevalence prior to a GCA diagnosis. The review found that PMR and hypertension were the comorbidities with the largest prevalence prior to GCA diagnosis. The strength of association between clinical features and a GCA diagnosis was stronger in this study than in the review, as has been described in sections 6.6.1.3 & 6.6.1.4.

There were differences in the results found in the review and those produced in this case-control study. There are numerous reasons why these differences occurred such as a difference between recording in primary care, where this study was conducted, and the secondary care setting of the articles included in the review. Another difference between this study and the articles included in the review was the time-period prior to GCA diagnosis that was examined. Most articles in the review recorded information on clinical features at the time of diagnosis/temporal artery biopsy. Few articles included the time at which clinical

features were recorded prior to GCA diagnosis. Difference in sample sizes, geographical populations, and comparator groups could also explain the difference between the odds ratios produced in this study compared to those found in the review, as most articles included in the review had small sample sizes, were conducted outside the UK, and used patients with a negative temporal artery biopsy as the comparator group as opposed to the general population used in this study. The final difference could be due to the way GCA was diagnosed. In the review, the majority of the articles used temporal artery biopsy to confirm a diagnosis, followed by the ACR 1990 criteria. The definition of GCA used in this study were Read codes and glucocorticoid prescription information. In UK primary care suspected GCA patients are referred to a specialist, usually a rheumatologist according to NICE guidelines, for further examination. Not all patients with GCA in the UK will undergo a temporal artery biopsy for confirmation of diagnosis, as ultrasound is also used to confirm a GCA diagnosis (NICE CKS, 2020). Therefore, the GCA population used in this review may not be the same as those used in the articles included in the review, and hence may produce different results.

6.6.2 Strengths and limitations

This study was conducted in a large primary care database, generalisable to the UK population, and included over 9000 patients diagnosed with GCA. Furthermore, due to the use of an EHR database, diagnosis of GCA did not rely on temporal artery biopsy alone, or on other less reliable methods of diagnosis (such as the ACR 1990 criteria). A strength of the analysis is that the results were robust to the definition of GCA and after adjustment for patient demographics, shown by the multiple sensitivity analyses conducted. The associations of clinical features and a subsequent GCA diagnosis were similar between GCA cases defined using only a Read code, and those defined using a Read code and a

prescription of glucocorticoids. GCA defined using Read code only produces a larger sample, but GCA defined using both Read codes and prescription information produces a more accurate sample since the recommended treatment for GCA are glucocorticoids which should be recorded in a patient's record. After restricting to patients only registered at practices in England, the results did not change. A final strength was the broad scope of clinical features that were investigated, with 14 being included in the analysis. These included all but one of the key features hypothesised to be associated with GCA. The only key feature that could not be mapped to a Read code was abnormal temporal artery.

There are several limitations relating to this investigation. Levels of missing data in patient demographics, either due to lack of recording, or historical values being lost when patients transfer between general practices. The missing category of both smoking status and alcohol consumption were the largest, composing of almost a third of cases, and almost half of controls. Conversely, for BMI it had the smallest amount of missing data for GCA cases, but almost a third of controls did not have a value recorded. Missing data is an acknowledged limitation of using resources such as CPRD, where there are numerous reasons for missingness. None of the missing variables can be reliably imputed using imputation techniques as they cannot be assumed to be missing at random (MAR), a key assumption of imputation methodology (as discussed in Chapter 4). The IMD 2015 score was missing for between 1% and 4% of cases and controls respectively in the subset of patients registered at practices in England who have linkage to IMD 2015. These are small amounts of missing data, and most likely would not have affected the results of the sensitivity analysis had they been complete.

A limitation regarding the definition of clinical features is that severity of symptoms is not recorded in primary care EHR. Frequency of consultations for clinical features were also not

assessed. A possibility for the associations found in the remaining comorbidities is surveillance bias. Patients who have chronic conditions have a higher number of consultations to primary care (Salisbury, Johnson, Purdy, Valderas, & Montgomery, 2011). This increased contact time with GPs may induce surveillance bias since these patients are more likely to be undergoing regular check-ups and blood tests.

6.6.3 Conclusions

Patients who eventually receive a GCA diagnosis are significantly more likely to consult primary care with any one of 14 different clinical features in the preceding 24 months. However, as the recorded prevalence of many of these clinical features remains infrequent in the GCA population and are frequently reported in relation to many other conditions in primary care, identifying GCA much earlier in the disease course remains a challenge. General symptoms such as fever and fatigue, with the "classical" symptoms such as headache, and comorbidities such as hypertension are all associated with a subsequent GCA diagnosis. The strength of association between symptoms and a GCA diagnosis are stronger the closer the symptom is to the date of diagnosis. This could indicate the possibility of a patient consulting multiple times for the same symptom over a short period of time, thereby prompting the GP to investigate further, which would lead to a GCA diagnosis. However, the association between comorbidities and GCA remain stable over time, with a spike at 6 months prior.

Overall, this study suggests patients may have at least 24 months between the first presentation of a clinical feature and a diagnosis of GCA, with symptoms first occurring closer to the date of GCA diagnosis than comorbidities. Although this study indicates which clinical features are associated with a diagnosis of GCA individually, the use of this

information is limited as it remains difficult for GPs to link isolated, some commonly occurring, clinical features 24 months prior to GCA. Therefore, the next step is to investigate clusters of clinical features in the 24 months prior to a diagnosis of GCA.

Chapter 7: Combinations of presenting clinical features

7.1 Chapter overview

This chapter details the methods and results of a latent class analysis (LCA) aiming to investigate whether there are distinct clusters of clinical features recorded in primary care prior to a diagnosis of GCA in the UK. A secondary objective of this chapter was to assess Latent Class Analysis (LCA) applied to primary care EHR as a method to derive patterns of clinical features in GCA.

7.2 Background

In the previous chapter, a case-control study was conducted to investigate the relationship of recorded clinical features in the previous 24 months with a diagnosis of GCA. Conditional logistic regression was used to explore this relationship to determine the independent association of each clinical feature with GCA. It was concluded that although many clinical features are associated with a GCA diagnosis, presenting with a single feature to primary care may not lead to a prompt diagnosis of GCA. Therefore, it is important to investigate combinations of clinical features which may help GPs more promptly consider the likelihood of GCA in the patient before them.

LCA has become an increasingly common methodology for health research due to its usefulness across diverse areas of clinical research and increasing availability of software (Kongsted & Nielsen, 2017). The use of LCA reaches across all health research areas, with studies published using LCA to quantify patterns of eating habits of families with teenage children (Schnettler et al., 2018), to that characterising the prodrome of rheumatoid arthritis (Muller et al., 2019).

In a study conducted by Sepriano et al (2020) to investigate the prodrome of axial spondyloarthritis (axSpA), a condition that is difficult to diagnose and prone to diagnostic delay (Sepriano et al., 2020), LCA was used to identify combinations of characteristics that would improve the classification criteria that currently exists regarding the diagnosis of axSpA. From a sample of 465 patients with axSpA, this study found that there were four distinct classes; no SpA, family history of axSpA but no features, inflammatory back pain and peripheral features prior to axSpA, and lesions present on axial imaging prior to axSpA. Due to LCA's methodological superiority over distance-based clustering techniques, described in section 7.4.2, and its previous use to identify clusters of patients presenting with conditions that are difficult to diagnose, it will be used for the analysis in this study.

7.3 Aim

The main aims of this study were to identify common patterns of clinical features that are presented to primary care by patients in the 24 months prior to their diagnosis of GCA, and to assess the value of LCA for deriving patterns of clinical features presented to primary care prior to a GCA diagnosis.

7.4 Methods

7.4.1 Study population & clinical features

Patients diagnosed with GCA from 1990-2017 were included in this study. Selection and patient eligibility has been described in Chapter 6, section 6.4.1. GCA cases from Chapter 6 were retained, with their matched controls being removed for this analysis. The clinical features included in this analysis have been discussed in Chapter 6, section 6.4.3. However, in brief, 14 clinical features were investigated and Read code lists were created for each of

these and mapped to CPRD's medcodes. The clinical features included in this chapter are; headache, fever, cancer, weight loss/anorexia, visual impairment, fatigue, treated hypertension, cardiovascular/cerebrovascular diseases, recorded elevated ESR, anxiety/depression, PMR, arthralgia/myalgia, diabetes, and jaw pain.

In the analysis conducted in Chapter 6, the time prior to GCA diagnosis was categorised by months prior to diagnosis; 24 months, 12 months, 6 months, and ≤1 months prior. For the latent class analysis, the full 24 months prior to a diagnosis of GCA was used as the analysis conducted in Chapter 6 highlighted that symptoms may present several months prior to a GCA diagnosis, and therefore using a period shorter than 24 months risks missing key early symptoms that may be relevant from the analysis. Chapter 6 also highlighted that the association of comorbidities with GCA were consistent over the 24 months prior to a GCA diagnosis. Given that chronic comorbidities, such as hypertension and diabetes, may not be recorded using a disease Read code on a regular basis, but rather through prescription codes for related medications, using a time-period of less than 24 months may also miss the presence of a comorbidity. The period from 24 months prior to a GCA diagnosis was the time-period with the largest prevalence of clinical features, thereby increasing the power of the analysis. It is also possible that clinical features recorded prior to 24 months may not be related to a GCA diagnosis (Talarico et al., 2020), and as discussed in Chapter 6 section 6.4.2.1, it was decided not to extend the analysis beyond the 24 months prior to a GCA diagnosis.

7.4.2 Analysis

A common method of identifying patterns and combinations in data are clustering techniques. There are many clustering techniques that can be implemented on data, but one

of the simplest is k-means. Most clustering techniques are based on methodology that involves measuring the distance between data points (in the case of health research these data points would be patients), and using this distance to group the patients into clusters (Brusco, Shireman, & Steinley, 2017). For example, with k-means, clusters are created based on how far a patient's data is from the estimated "centroid" of a cluster, also called the mean of the cluster. Patients who are close to the cluster centroid are assumed to be in that cluster (Brusco et al., 2017). K-means is an iterative process. The algorithm begins with random data points as centroids, and with each iteration these centroids are moved until either the optimal centroid has been found, or the algorithm has completed the number of iterations it was programmed to complete. Most clustering techniques beyond k-means are based on the same methodology of calculating the distance between data points and using these distances to allocate data to clusters. The disadvantage of these techniques is the lack of repeatability. Due to the process being iterative it is difficult to reach the same results each time the algorithm is run, and hence there may be a lack of consistency between one set of results and the next (Raykov, Boukouvalas, Baig, & Little, 2016). Another disadvantage, and the one that makes k-means unsuitable for use in this study, is that k-means assumes all clusters to be of the same size (Raykov et al., 2016). A further limitation of clustering techniques is their inability to assess the strength of cluster classification, and the lack of available model fit assessment criteria (Raykov et al., 2016).

An alternative to distance-based clustering techniques is a modelling-based approach that uses probability methodology to allocate data into classes. Latent class analysis (LCA) is a mixture modelling technique that can be used to investigate common groups of presenting features in GCA. LCA classifies individuals into groups, called latent classes, based on categorical responses. In the case of this study these responses are the primary care

recorded clinical features (binary variable: recorded or not recorded) prior to the date of GCA diagnosis. LCA assumes homogeneity within clusters, i.e. patients within each cluster should have similar recorded features, and heterogeneity between clusters, i.e. patients in different clusters should have different patterns of recorded features.

Latent class models are a form of finite mixture models, where all variables are assumed to be independent within each cluster, also called local independence (Beath, 2017; Linzer & Lewis, 2011). Assume that there are *J* polytomous categorical variables observed (in this case J = 14 clinical features), and each contains *K* possible outcomes (in this case K = 2, corresponding to the clinical feature being recorded or not recorded), for individuals *i = 1,….,N*. The observed values of the *J* categorical variables are denoted by the binary Y_{ijk}, where Y_{ijk} = 1 if respondent *i* gives the k^{th} response to the j^{th} variable, and Y_{ijk} = 0 otherwise, for *j = 1…., 14*, and *k = 1,..2*.

Let R denote the number of classes in the latent class model, which is chosen based on theoretical and practical reasons, i.e. a combination of model fit and clinical opinion, as discussed in section 7.4.2.1. There are two key parameters estimated by the latent class model. The first is the probability of having a recorded clinical feature (class-conditional outcome probability) within each class *r = 1,…, R,* denoted by π_{jrk}. The sum of these class-conditional probabilities, within each class, is equal to one. The second are prior probabilities of latent class membership and are defined as the probability that an individual will belong to a class prior to observing their response to the categorical variables (Y_{ijk}), and is denoted as p_r.

The formula of a latent class model is given by:

$$f(Y_i; \pi_r) = \prod_{j=1}^{J} \prod_{k=1}^{K_j} (\pi_{jrk})^{Y_{ijk}} \quad (4)$$

The posterior probability of each individual belonging to each class in the model is the probability of class membership given each individual's recorded clinical features, and is given by the following formula:

$$\hat{P}(r_i|Y_i) = \frac{\widehat{p_r}\, f(Y_i;\widehat{\pi_r})}{\sum_{r=1}^{R} \widehat{p_r}\, f(Y_i;\widehat{\pi_r})} \quad (5)$$

Where $r_i \in \{1,\ldots,R\}$, and $\widehat{p_r}$ and $\widehat{\pi_r}$ are the estimates of the prior probabilities and probability of having a clinical feature recorded conditional on class membership, respectively. Latent class models are estimated by maximising the log-likelihood function.

Latent class models produce class conditional outcome probabilities for each variable included in the model, in the case of this study for each clinical feature. These probabilities are considered high if they are >70%, i.e. the probability of a patient allocated to a cluster having that clinical feature is over 70%. If a clinical feature has a conditional outcome probability of higher than 70%, it can be considered a key feature of that class (Beath, 2017; Linzer & Lewis, 2011). If a clinical feature has a conditional outcome probability of 50%, then half of the people in the cluster are estimated to have that clinical feature, and half not, and hence it does not help to define the cluster.

The recommended practice for LCA is to fit a small number of classes initially, such as 1 or 2, and increase the number of classes by one in every iteration until the best fitting and/or most clinically relevant model is found (Linzer & Lewis, 2011). Therefore, initially a 2-class model will be fitted to the data for the 24 months prior to a diagnosis of GCA, with each subsequent model including one more class than the previous. The optimal number of classes fitted to the data depends on the model fit statistics when comparing a model to the model with one less class, as described in section 7.4.2.1.

If, by increasing the number of classes, the fit statistics become worse, then the iterative process should stop as the best model has already been found (Mueller et al., 2017). The average posterior probability of each class should also be taken into account when assessing model fit, as the smaller the value (usually less than 0.7) indicates that separation between classes is poor, and therefore may not be the most appropriate model (Mueller et al., 2017). That is, patients have on average less than 70% probability of being in the class they have been allocated to. However, the most statistically relevant model may not be the most clinically relevant. Therefore, a compromise needs to be reached between model fit and clinical applicability and this was achieved through discussion with the wider supervisory team after taking into account the goodness of fit statistics, average posterior probabilities, and class conditional outcome probabilities.

Each latent class model was run 100 times using randomly generated starting values for 3000 iterations so that the global maximum likelihood could be found (Linzer & Lewis, 2011). All analysis was conducted using the PoLCA package in R studio v3.4.2 (Linzer & Lewis, 2011; R Core Team, 2017).

7.4.2.1 Model assessment

With every increase in the number of classes, the risk of producing an over-fitting model increases (Linzer & Lewis, 2011). The purpose of model assessment criteria is to find an optimum model that is neither under-fitted (does not explain the associations in the data well) nor over-fitted (explains the data too well and is therefore not generalisable to other data). The most commonly reported goodness of fit methods for LCA model assessment are Akaike's Information Criteria (AIC) and Bayesian Information Criteria (BIC) (Beath, 2017). Other model fit assessment methods include the "consistent" AIC (CAIC) and the bootstrap

likelihood ratio test (BLRT). The CAIC is an alternative to the AIC, and is less affected by a change in sample size (Anderson, Burnham, & White, 1998). The BLRT is an alternative to the likelihood ratio test (LRT), which cannot be used to assess LCA models due to distribution assumptions being violated by the LCA methodology (Tekle, Gudicha, & Vermunt, 2016). Bootstrapping has been suggested to empirically generate a model distribution that would not violate the LRT's assumptions and would instead use the maximum likelihood estimate produced by the LCA model (Tekle et al., 2016). Both the CAIC and BLRT could not be calculated from the software used to run this analysis. However, the BIC is commonly accepted as the optimal model assessment criteria for LCA (Nylund, Asparouhov, & Muthén, 2007). Hence, the AIC, BIC, and relative entropy (described below) were used to assess overall model fit, and the average posterior probability used to assess individual class fit.

If we let *L* represent the maximum log-likelihood of the latent class model, and Φ the number of estimated parameters, then the AIC and BIC are defined as:

$$AIC = -2L + 2\Phi$$

$$BIC = -2L + \Phi \ln(N)$$

N is the total sample size. The BIC, AIC, relative entropy, and average posterior probability for each class, will be considered and used in conjunction with clinical assessment to select the optimum model. Smaller values of AIC and BIC indicate a better fitting model.

7.4.2.2 Class assessment

Three criteria were used to select the optimum latent class model (Table 7.1). Relative entropy is a fit statistic that takes a value between 0 and 1, and indicates how distinct each class is from the others. It is calculated via the following formula:

$$Entropy = 1 - \frac{-\sum_{i=1}^{N}\sum_{r=1}^{R}\hat{P}(r_i|Y_i)*\ln(\hat{P}(r_i|Y_i))}{Nlog(R)} \quad (6)$$

$\hat{P}(r_i|Y_i)$ is the conditional posterior probability for each individual *i = 1,…,N*, and represents the probability of membership in each of the *R* latent classes. An indicator of good model fit is an entropy value approaching 1 (Celeux & Soromenho, 1996).

Table 7.1: Criteria for choosing the optimum latent class model.

	Criteria	Requirement for good model fit
Model fit	1. BIC 2. AIC 3. Relative entropy	1. A smaller value 2. A smaller value 3. Close to 1
Class separation	Average posterior probability	Values closer to 1 (preferably ≥0.7) indicate good class separation.
Clinical assessment	Discussion with the wider supervisory team (epidemiologist, statistician, and a GP) to assess which model is the optimal based on statistical evidence, comparison between models, and clinical assessment.	

To assess class separation (definition) the average posterior probability of each class was calculated. The average posterior probability, as discussed in section 7.4.2, is the mean of the posterior probabilities for each individual allocated to that class, and is on a scale from 0 to 1, where a value closer to 1 (usually operationalised as ≥0.7) indicates a better class fit as individuals have a high probability of belonging to their allocated class (Linzer & Lewis, 2011; Mueller et al., 2017).

7.4.2.3 Demographics

Once patients have been assigned to a class, demographics (gender, age at diagnosis, BMI, smoking status, and alcohol consumption) were investigated for each class to investigate if these vary across latent classes and provide an overview of the patients allocated to each

class. The mean and median age at diagnosis for each class were calculated and compared, in conjunction with the proportion of males and females. BMI, smoking status, and alcohol consumption will be categorised, as has been described in Chapter 6 section 6.4.3, and the proportion in each category compared across all classes.

7.4.2.4 Sensitivity analysis

A sensitivity analysis was conducted grouping fever, weight loss/anorexia, and fatigue together under the heading of "constitutional symptoms" to reflect that these symptoms are commonly combined, and can all be considered constitutional symptoms. All models will be assessed via model fit statistics for latent class analysis as discussed above.

7.5 Results

7.5.1 Sample characteristics

The total number of patients with GCA included in this analysis was 9205. Demographics of this population have been detailed in Chapter 6, section 6.5.1. In brief, the mean age of the sample was 72.6 years (SD = 10.3), and 71% were female.

7.5.2 Latent class analysis

A comparison of fit between LCA models with different numbers of classes fitted to the 24-month data can be seen in Table 7.2. Each model fit criteria suggested a different model to be the optimum. The AIC was smallest for the 6-class model, whereas the BIC was smallest for the 4-class. The relative entropy was the largest (i.e. the closest to 1) for the 3-class model. The AIC continued to decrease the more classes were added to the model, and hence was not considered to be a reliable method to choose the final model. In order to decide

which model was the best the average posterior probabilities for each model were examined, and the clinical relevance of classes with the 3, 4, and 5-class models were discussed with the supervisory team. The average posterior probabilities were best for the 3-class model as all were above the accepted threshold of 0.7. Only two of the classes in the 4-class model were above this threshold, and three in the 5-class model. After discussion with the supervisory team, it was decided that the 5-class model was the most clinically relevant as the fourth and fifth classes identified potentially important subgroups of GCA patients that the 3-class model did not. Comparisons of the chosen 5-class model to the 3-class model is given in 7.5.2.1.

Table 7.2: Model comparison between the 2 through 6-class LCA models on the 24 months prior to a GCA diagnosis. Final model shown in bold.

Model	AIC	BIC	Relative entropy
2-class	81498.14	81704.84	0.473
3-class	81217.13	81530.74	0.690
4-class	81097.51	81518.03	0.587
5-class	**81017.39**	**81544.82**	**0.676**
6-class	80990.69	81625.04	0.584

In the chosen 5-class model, the first class contained 2485 (27.00%) patients. The average posterior probability was 0.98, indicating good class fit. There was no clinical feature in this class that had a conditional outcome probability of more than 70%, indicating that this class had no dominating presenting feature (Table 7.3). The clinical feature with the highest estimated conditional outcome probability was headache (39.23%), followed by treated hypertension (25.70%). The conditional outcome probabilities for the remaining 12 clinical features were all less than 10%. The median number of clinical features prior to a GCA diagnosis for patients in this class was 1 (IQR = 1), and 995 (40.04%) patients allocated to this

class only consulted with one clinical feature, and 1031 (41.49%) consulted with no clinical features prior to their GCA diagnosis (Table 7.4). This class was labelled as “Single or no feature”.

The second class contained 1968 (21.38%) patients. The average posterior probability for this class was 0.76, indicating good class fit. The most common feature was recorded elevated ESR, followed by headache and hypertension. Patients in this class had a median of 1 (IQR = 1) recorded clinical feature prior to their GCA diagnosis, and the majority (43.19%) of patients had 1 clinical feature prior to their GCA diagnosis (Table 7.4). This class was labelled “Elevated ESR”.

The third class contained 500 (5.43%) patients. The average posterior probability was 0.65, indicating moderate class fit. The dominating feature of this class was treated hypertension, followed by headache (Table 7.3). The median number of clinical features prior to a GCA diagnosis for patients in this class was 4 (IQR = 2), with a minimum of 3 clinical features prior to GCA diagnosis (Table 7.4). This class was labelled as “hypertension + multiple other features”.

The fourth class was the largest and contained 3285 (35.69%) of patients. The average posterior probability was 0.63, indicating moderate class fit. Every patient allocated to this class had treated hypertension prior to their GCA diagnosis (Table 7.3). The median number of clinical features prior to GCA diagnosis for patients in this class was 2 (IQR = 2). 949 (28.89%) patients in this class had treated hypertension only prior to their GCA diagnosis, and 1348 (40.04%) patients had one other clinical feature (in addition to treated hypertension) prior to their GCA diagnosis (Table 7.4). This class was labelled “hypertension”.

The fifth class contained 967 (10.51%) patients. The average posterior probability for this class was 0.76, indicating patients in this class were generally clearly allocated to this class (Table 7.3). All patients allocated to this class had a record of PMR prior to their GCA diagnosis. The median number of clinical features prior to GCA diagnosis for patients in this class was 2 (IQR = 1). 174 (17.99%) patients in this class had PMR only prior to their GCA diagnosis, and 369 (38.16%) patients had 1 other clinical feature (in addition to PMR) (Table 7.4). This class was labelled “PMR”.

Table 7.3: LCA model results for the 5-class final model, showing class conditional outcome probabilities.

	Class 1 – Single or no feature (n = 2485 (27.00%))	**Class 2 – Elevated ESR (n = 1968 (21.38%))**	**Class 3 – Hypertension + multiple other features (n = 500 (5.43%))**	**Class 4 – Hypertension (n = 3285 (35.69%))**	**Class 5 – PMR (n = 967 (10.51%))**
	Class conditional outcome probability	Class conditional outcome probability	Class conditional outcome probability	Class conditional outcome probability	Class conditional outcome probability
Headache	39.23%	55.01%	57.72%	39.35%	30.03%
Fever	0.62%	0.42%	2.64%	0.11%	0.00%
Cancer	3.42%	3.84%	5.55%	4.96%	3.71%
Weight loss	2.20%	2.20%	11.40%	0.58%	2.82%
Visual	3.28%	2.59%	6.03%	2.40%	3.24%
Fatigue	6.24%	9.13%	26.31%	3.67%	10.04%
Treated hypertension	25.70%	38.26%	96.91%	100.00%	50.01%
Cardiovascular diseases	4.10%	2.67%	37.93%	22.90%	3.89%
Elevated ESR	0.04%	99.79%	41.94%	23.33%	45.65%
Anxiety/Depression	7.18%	5.17%	17.57%	7.36%	5.22%
PMR	1.27%	3.01%	13.42%	4.89%	100.00%
Arthralgia/Myalgia	4.94%	5.56%	15.06%	3.92%	23.14%
Diabetes	3.07%	5.57%	21.66%	19.79%	7.18%
Jaw pain	1.60%	3.23%	2.73%	1.38%	2.12%

Key: Dark red indicates dominating class features (features with the highest conditional outcome probability); orange indicates features with the highest outcome probability, but below cut-off of 70%.

Table 7.4: Number of recorded consultations prior to a GCA diagnosis for each class.

	Class 1 – Single or no feature (n = 2485)	**Class 2 – Elevated ESR (n = 1968)**	**Class 3 – Hypertension + multiple other features (n = 500)**	**Class 4 – Hypertension (n = 3285)**	**Class 5 – PMR (n = 967)**
Mean number of clinical features prior to GCA diagnosis (SD)	0.81 (0.83)	1.38 (0.89)	4.06 (1.01)	2.07 (0.88)	2.43 (1.00)
Median number of clinical features prior to GCA diagnosis (IQR)	1 (1)	1 (1)	4 (2)	2 (2)	2 (1)
Number of clinical features prior to GCA diagnosis	**Number of patients (%)**	**Number of patients (%)**	**Number of patients (%)**	**Number of patients (%)**	**Number of patients (%)**
0	1031 (41.49%)	298 (15.14%)	0	0	0
1	995 (40.04%)	850 (43.19%)	0	949 (28.89%)	174 (17.99%)
2	372 (14.97%)	612 (31.10%)	0	1348 (40.04%)	369 (38.16%)
3	79 (3.18%)	187 (9.50%)	168 (33.60%)	808 (24.60%)	285 (29.47%)
4+	8 (0.32%)	21 (1.07%)	332 (66.40%)	180 (5.48%)	139 (14.37%)

7.5.2.1 Comparison to 3 and 4-class models

As described in section 7.5.2, the optimal model was different for each model selection criteria. The 5-class model was chosen after discussion with the wider supervisory team. However, the 5-class model did not have the best average posterior probabilities for each class and had poorer model fit based on AIC and entropy. The three classes in the 3-class model were the "PMR" class, with an average posterior probability of 0.85, a "Single or no feature" class with an average posterior probability of 0.83, and a "hypertension + multiple other features" class with an average posterior probability of 0.76. The classes the 3-class model did not define were the "hypertension" and "Elevated ESR" classes.

The 4-class model has one of the smallest AIC values. The classes produced in the 4-class model ("PMR", "hypertension + multiple other features", and "Single or no feature", and a fourth class which was similar to the "Single or no feature") were mostly defined in the 5-class model. The average posterior probabilities for these classes were lower in the 4-class model than in the 5-class model. Two of the four classes had no dominating feature, and only two classes had an average posterior probability of over 70%.

7.5.2.2 Class demographics

The first class, named "Single or no feature", were on average the youngest class, with a mean age of 68.90 years (SD = 11.33), and a median of 70 years (IQR = 16). 38.59% were under/normal weight (Table 7.5). The second class, named "Elevated ESR", had a mean age of 73.34 (SD = 9.55), and a median of 74 (IQR = 13) years. 40.45% were under/normal weight; 29.07% were non-smokers; and 36.03% were light drinkers. The third class, named "Hypertension + multiple other features", were on average the oldest class, with a mean age of 74.65 years (SD = 9.31), and a median of 76 years (IQR = 12). 36.80% were under/normal

weight; 32.40% were non-smokers; and 34.00% were light drinkers. The fourth class, named "hypertension" had a mean age of 74.30 years (SD = 9.89), and a median age of 75 years (IQR = 13). 33.73% of this class were overweight; 31.87% were non-smokers; and 34.28% were light drinkers. The fifth class, named "PMR", had a mean age of 73.35 years (SD = 8.50), and a median age of 73 years (IQR = 13). 39.71% were under/normal weight, and 35.16% were light drinkers (Table 7.5).

Table 7.5: Class demographics for the 5-class LCA model.

	Class 1 – Single or no feature		**Class 2 – Elevated ESR**		**Class 3 – Hypertension + multiple other features**		**Class 4 – Hypertension**		**Class 5 – PMR**	
	N	%	N	%	N	%	N	%	N	%
N	2485	27.00	1968	21.38	500	5.43	3285	35.69	967	10.51
Average posterior probability	0.98		0.76		0.65		0.63		0.76	
Males	805	32.39	512	26.02	115	23.00	1030	31.35	211	21.82
Females	1680	67.61	1456	73.98	385	77.00	2255	68.65	756	78.18
Mean age at diagnosis (SD)	68.90 (11.33)		73.34 (9.55)		74.65 (9.31)		74.30 (9.89)		73.35 (8.50)	
Median age at diagnosis (IQR)	70 (16)		74 (13)		76 (12)		75 (13)		73 (11)	
BMI										
Normal/under	959	38.59	796	40.45	184	36.80	890	27.09	384	39.71
Overweight	727	29.26	675	34.30	156	31.20	1108	33.73	323	33.40
Obese	373	15.01	313	15.90	121	24.20	917	27.91	174	17.99
Missing	426	17.14	184	9.35	39	7.80	370	11.26	86	8.89
Smoking										
Non-smoker	774	31.15	572	29.07	162	32.40	1047	31.87	340	35.16
Current	396	15.94	326	16.57	65	13.00	471	14.34	113	11.69
Ex	517	20.80	569	28.91	149	29.80	964	29.35	257	26.58
Missing	798	32.11	501	25.46	124	24.80	803	24.44	257	26.58
Alcohol										
None	330	13.28	307	15.60	77	15.40	553	16.83	137	14.17
Light	827	33.28	709	36.03	170	34.00	1126	34.28	372	38.47
Moderate	248	9.98	202	10.26	46	9.20	317	9.65	105	10.86
Heavy	196	7.89	147	7.47	23	4.60	220	6.70	56	5.79
Missing	884	35.57	603	30.64	184	36.80	1069	32.54	297	30.71

7.5.2.3 Sensitivity analysis

The sensitivity analysis included "constitutional symptoms" as a variable rather than the three individual symptoms. The model with the smallest AIC was the 6-class, and the 4-class model had the smallest BIC and largest entropy (Table 7.6). However, to allow comparability between this sensitivity analysis and the main analysis, the 5-class model is presented. Results from the 4-class model can be seen in Appendix 7.1, Table 3.

Table 7.6: Model comparison from the sensitivity analysis combining constitutional symptoms on the 24 months prior to a GCA diagnosis.

Model	**AIC**	**BIC**	**Relative entropy**
2-class	79621.56	79799.74	0.681
3-class	79348.70	79619.55	0.690
4-class	79230.22	79593.73	0.734
5-class	79169.44	79625.60	0.676
6-class	79142.80	79691.62	0.572

The first class contained 2538 (27.57%) patients (

Table 7.7). There was no dominating feature of this class. The clinical feature with the highest outcome probability was headache at 39.27%. The median number of clinical features prior to a GCA diagnosis for patients in this class was 2 (IQR = 1), hence this class corresponds to the "Single or no features" class found in the main analysis. Constitutional symptoms had a class conditional outcome probability of 8.83%.

The second class contained 941 (10.22%) patients (

Table 7.7). Every patient allocated to this class had PMR. This class corresponds to the "PMR" class found in the main analysis and will be labelled similarly. Patients in this class had an 11.98% probability of having constitutional symptoms.

The third class contained 576 (6.26%) patients (

Table 7.7). The dominating features of this class were treated hypertension with a class conditional probability of 98.12%, and headache with a probability of 55.42%. This class corresponds to the "hypertension + multiple other features" found in the main analysis. This was the class with the highest probability of constitutional symptoms, at 34.65%.

The fourth class contained 1972 (21.42%) patients. The dominating feature of this class was recorded elevated ESR, with a class conditional outcome probability of 99.93%. This class corresponds to the "Elevated ESR" class found in the main analysis. Constitutional symptoms had a class conditional outcome probability of 11.45%.

The fifth class contained 3178 (34.52%) patients (

Table 7.7). Everyone in this class had a record of treated hypertension. This class corresponds to the "hypertension" class found in the main analysis, and was labelled similarly. Constitutional symptoms had a class conditional outcome probability of 3.55%.

Table 7.7: Model output from the 5-class LCA sensitivity model. Clinical feature with the largest probabilities are highlighted.

	Class 1 – Single or no features (n = 2538 (27.57%))	**Class 2 – PMR (n = 941 (10.22%))**	**Class 3 – Hypertension + multiple features (n = 576 (6.26%))**	**Class 4 – Elevated ESR (n = 1972 (21.42%))**	**Class 5 – Hypertension n = 3178 (34.52%))**
	Class conditional outcome probabilities	Class conditional outcome probabilities	Class conditional outcome probabilities	Class conditional outcome probabilities	Class conditional outcome probabilities
Headache	39.27%	29.51%	55.42%	55.00%	39.43%
Cancer	3.42%	3.70%	5.53%	3.85%	4.97%
Visual	3.31%	3.20%	6.07%	2.58%	2.18%
Treated hypertension	26.77%	49.81%	98.12%	38.72%	100.00%
Cardiovascular diseases	4.18%	3.68%	36.91%	2.75%	23.09%
Elevated ESR	0.16%	45.41%	41.65%	99.93%	22.72%
Anxiety/depression	7.20%	5.11%	16.61%	5.23%	7.27%
PMR	15.20%	100.00%	14.58%	3.47%	4.41%
Arthralgia/Myalgia	4.97%	23.43%	14.48%	5.59%	3.67%
Diabetes	3.11%	7.17%	21.71%	5.65%	20.05%
Jaw pain	16.10%	2.07%	2.64%	3.22%	1.35%
Constitutional symptoms	8.83%	11.98%	34.65%	11.45%	3.55%
Mean number of Clinical features (SD)	1.38 (0.89)	0.84 (0.84)	4.33 (1.07)	2.16 (1.00)	2.83 (1.11)
Median number of Clinical features (IQR)	1 (1)	2 (1)	4 (1)	2 (2)	3 (2)

Key: Dark red indicates dominating class features (features with the highest conditional outcome probability); orange indicates features with the highest outcome probability, but below cut-off of 70%.

7.5.2.4 Comparison to the 4-class model

The 4-class model had the largest relative entropy and the smallest BIC, and therefore was statistically the most appropriate. The four classes found in this model were the "PMR" class with an average posterior probability of 0.78, "hypertension + multiple other features" with an average posterior probability of 0.83, "Single or no features" with an average posterior probability of 0.80, and "Elevated ESR" with an average posterior probability of 0.71 (Appendix 7.1, Table 3). The class that was not included in the 4-class model was the "hypertension" class.

7.6 Discussion

This study found that there are five distinct classes of clinical features that patients present with in the 24 months prior to their diagnosis of GCA ("Single or no features", "hypertension", "PMR", "Elevated ESR", and "hypertension + multiple other features"). Patients with GCA in both the "PMR", "Single or no features", and "Elevated ESR" classes were, on average, younger than the "hypertension", and "hypertension + multiple other features" classes, and more likely to have lower BMI. The classes with treated hypertension as a dominant feature were more likely to be older, and have higher BMI. This is possibly due to the association between BMI and hypertension, with patients classified as being overweight or obese having higher risk of hypertension than someone who is of normal weight (Landi et al., 2018).

These results confirm that headache, PMR, recorded elevated ESR, and hypertension are common features in patients diagnosed with GCA. The results of Chapter 6 have shown that these features are strongly associated with a GCA diagnosis. Although in this analysis headache was not the dominating feature of all classes, it was the most prevalent in the

"Single or no features" class, whilst being the second most prevalent after treated hypertension in the "hypertension" and "hypertension + multiple other features" classes, elevated ESR in the "elevated ESR" class, and PMR in the "PMR" class. Patients with PMR formed their own class where all patients in that class had PMR prior to their GCA diagnosis. Hypertension is known to be highly prevalent in this age group for both sexes (Alfie & Cuffaro, 2019), and similarly to headache, a patient presenting with hypertension will not always go on to have a diagnosis of GCA. Previous studies have established hypertension as a risk factor for visual loss in GCA (C Dejaco, Duftner, Buttgereit, Matteson, & Dasgupta, 2017; Patil et al., 2015), although these patients tended to be older, and male. Previous studies investigating hypertension as a risk factor for GCA have produced varying conclusions. A study investigating the association between cardiovascular risk factors, such as elevated diastolic blood pressure, smoking, and high sensitivity C-reactive protein (hs-CRP), and incident GCA found only smoking was a risk factor for incident GCA (Yates et al., 2020), although only 118 GCA cases were included in this study. Another study investigated the difference in features of GCA between patients over 75 years of age and found that more of these patients had history of cardiovascular conditions and high blood pressure than patients younger than 75 years of age (Daumas et al., 2019). A study conducted in Iceland found that hypertension was a risk factor for GCA in males, but not females, and that having higher BMI and having ever smoked (risk factors for cardiovascular conditions) were protective factors for incident GCA (Tomasson, Bjornsson, Zhang, Gudnason, & Merkel, 2019). These findings could suggest that new onset hypertension, or a sudden increase in blood pressure or loss of control of existing hypertension, may be an early indicator for incident GCA in patients who are older.

Clinical features that were highly associated with a diagnosis of GCA in Chapter 6, such as constitutional symptoms, visual impairment, and jaw pain, did not form a distinct part of any cluster produced in this analysis. Each class produced had a low probability of jaw pain, visual impairment, fatigue, fever, weight loss/anorexia independently, and for the grouped variable of constitutional symptoms included as a sensitivity analysis. These features were associated with a GCA diagnosis in Chapter 6, but the prevalence of all these clinical features was low in the population. Reasons for the low prevalence may be because they are not commonly coded in a patient's record, as GPs may record other more prominent symptoms, or record them in the free-text section. In the case of jaw pain, a patient may initially consult a dentist, and with visual impairment a patient may initially consult an optician. An alternative is that these symptoms are ignored during a consultation, or not brought up by the patient. A final alternative is that patients simply do not present with these or multiple clinical features prior to their GCA diagnosis.

7.6.1 Clinical applicability

These findings demonstrate that the number of clinical features a patient presents with prior to their GCA diagnosis can vary from none to multiple. Headache is still a prevalent presenting feature but may not always indicate a GCA diagnosis. This study has highlighted a possible association between hypertension and a subsequent diagnosis of GCA, despite previous research on this relationship producing conflicting findings. Further studies are needed to investigate this relationship. Patients who are diagnosed with PMR should be continually monitored for GCA and counselled of its association with PMR so they seek help early should GCA symptoms develop. Ideally, further studies would be needed to see if these

clusters can be replicated and to understand better how they can be incorporated into guidance and clinical care.

7.6.2 Strengths and limitations

The main strength of this study is that it is the first to examine combinations of (14) clinical features, in contrast to previous studies that have focused on clinical features in isolation.. The large sample size of this study, including over 9000 GCA patients, and the breadth of the analysis where the classes produced were robust to changes in the definition of a GCA case, are further strengths of this study.

A limitation of the analysis was that not all assumptions of the LCA could be assessed. The main assumption of LCA is local independence, that the clinical features were independent within each cluster. The method of checking the local independence assumption is through examining bivariate residuals. A limitation of the software used to perform this analysis was that the bivariate residuals were unable to be extracted from the model output, and hence the local independence assumption could not be checked. However, the observed patterns for patients in each cluster reflects closely the overall cluster pattern, which gives sustenance to the clusters found in this study being the “true” clusters.

A further methodological limitation was that only certain model assessment criteria could be produced by the software. This study used the BIC and AIC to assess model fit. However, there are more available in other LCA software, such as the BLRT and the CAIC, described in section 7.4.2.1, that were not available in the software used to conduct this analysis. The BLRT and CAIC have few advantages over the AIC and BIC, and both the AIC and BIC are more commonly reported in previous studies, and it is generally accepted that the BIC is superior when considering LCA model fit (Mueller et al., 2017; Nylund et al., 2007; Sepriano et al.,

2020). It is also unlikely that other model fit criteria would have suggested a different number of classes. There was little difference between the classes produced in the 3 and 4-class models and the final 5-class model. The 3-class model, although better regarding class fit, missed an important class of patients whose defining feature was treated hypertension.

7.6.3 Conclusions

Patients with GCA can be categorised into five distinct classes, based on the clinical features that are recorded in GP records within the 24 months preceding their diagnosis. There are distinct clinical features that dominate these clusters, including headache, treated hypertension, elevated ESR, and PMR. However, these are rarely in combination with another clinical feature. Next steps regarding the classes found in this study could be to test their overall generalisability by assessing whether these are replicated in other primary care EHR datasets, such as CPRD Aurum, or THIN. Additionally further research on clinical applicability would be required. Overall, LCA methodology has value for deriving patterns of presenting clinical features in primary care and is worth pursuing in further research around GCA and other conditions.

Chapter 8: Discussion

8.1 Chapter summary

The aim of this thesis was to quantify the prevalence and association of clinical features with a subsequent diagnosis of GCA. This chapter will discuss the findings of the studies conducted in this thesis, detailing strengths and limitations, areas for future research, and applicability to clinical practice.

8.2 Overall findings of the thesis

8.2.1 The role of individual clinical features on a diagnosis of GCA

The cohort study investigated trends in the consultation incidence and prevalence of GCA in the UK between 1990 and 2017 to establish the current burden of GCA in the UK population. The results showed that, overall, there was a small decrease in the consultation incidence of GCA in the UK between 1992 and 2017, with the exception of a small increase in the early 2000s. The highest consultation incidence rate was found in females between the ages of 70 and 79 years, with females having consistently higher consultation incidence rates than men. Despite the small decrease in incidence in the UK population in recent years, there remain many patients who develop this medical emergency in the UK population and therefore who need to be identified promptly to allow subsequent management and treatment in primary care. In particular, it is important that patients in the group shown to have the highest incidence rate are identified quickly, and determining the clinical features which are associated or indicative of a subsequent GCA diagnosis is imperative.

The systematic review and meta-analysis to examine the relationship between individual clinical features and a subsequent GCA diagnosis identified 31 clinical features studied in

relation to GCA. Clinical features most commonly observed in GCA patients prior to a diagnosis were headache, elevated ESR, and constitutional/systemic symptoms, and those with the strongest positive association with a diagnosis of GCA were jaw claudication, elevated ESR, and anorexia.

Of the 31 clinical features identified in the systematic review and meta-analysis, it was possible to examine 14 of these in the case-control study (Table 8.1). The clinical features with the highest prevalence in this study sample was again headache, but this time also treated hypertension. Other clinical features that were prevalent in this sample were elevated ESR, and constitutional symptoms, similar to the results found in the systematic review. Features with the strongest association with GCA in the case-control study were headache, treated hypertension, visual impairment, and PMR. Comorbidities had a weaker association to a GCA diagnosis than symptoms. The case-control study found that the association between a symptom and a GCA diagnosis was stronger the closer the symptoms occurred to the date of GCA diagnosis. It was also able to assess the time between when the feature was first recorded and the date of GCA diagnosis (diagnostic delay). Within 2 years of GCA diagnosis, the clinical features with the shortest time from recorded onset to diagnosis were headache, jaw pain, and visual symptoms. Comorbidities had longer times from first recorded onset to GCA diagnosis, with the shortest time being between PMR onset and GCA diagnosis. These results imply that symptoms are generally better indicators of imminent GCA, in that they occur closer to formal diagnosis, and certain comorbidities may be helpful associations to better understand GCA since they occur earlier than symptoms.

8.2.2 The role of patterns of clinical feature on subsequent GCA diagnosis

The cohort study investigated classes of clinical features that patients presented to primary care with prior to their diagnosis of GCA. Overall, five classes were identified; “PMR”, “Hypertension + multiple other features”, “Hypertension”, “Single or no features”, “Elevated ESR”. The “Single or no features” class contained patients who had none or one recorded clinical features in the 2 years prior to their GCA diagnosis. The PMR class contained patients who had PMR prior to their diagnosis of GCA. The elevated ESR contained patients who had elevated ESR prior to their GCA diagnosis. Hypertension was the dominating feature of the remaining two classes, and patients in these classes had more than one recorded clinical feature prior to their GCA diagnosis.

The results of this analysis showed that headache continues to be an important clinical feature, with a strong independent association with GCA, and in conjunction with other associated clinical features as it was prevalent in all of the classes found in the analysis. Hypertension, showed to be highly prevalent and strongly associated on its own with a GCA diagnosis, was also important at a combined level with other clinical features and was prominent in two of the four classes found. Previously associated features such as constitutional symptoms and jaw pain were not prominent features in any of the classes found in this analysis, hence they may have more value as indicators of GCA on their own rather than in conjunction with other clinical features. However, our findings do not necessarily negate their use in clinical practice given limitations relating to practitioner coding as discussed previously. This study serves as a starting point for further research that can validate the generalisability of the clusters found in this analysis.

Table 8.1: Summary table of the findings of this thesis and recommendations for areas of future work.

Clinical Feature	**Systematic review findings**		**Findings from electronic health records**	**Conclusions & recommendations**
	Prevalence	**Association**		
Headache	High	Strong positive (Odds Ratio > 1)	• Moderately high prevalence • Strong association with GCA diagnosis. • High proportion of GCA patients in each class had record of presenting with headache	• Headache has been established as an indicator of GCA • However, focus should move away from regarding it as the only clinical feature indicative of GCA
Elevated ESR	High	Strong positive	• Low recorded prevalence • Strong association with GCA diagnosis	• ESR should continue to be recorded for patients with suspected GCA • Improvement needed for coding in primary care records
Hypertension	Moderate/low	Not enough data	• High prevalence • Strong association with a GCA diagnosis • Two of the four classes of clinical features were predominately patients who had been treated for hypertension	• Few previously published articles have included hypertension as a clinical feature • Results from this thesis have shown there is a possible strong association between hypertension and a GCA diagnosis • Further research is required
PMR	Moderate/low	Moderate positive (non-statistically significant)	• Low prevalence • Strong positive association with a diagnosis of GCA • A clear class of patients who had predominately PMR prior to their GCA diagnosis	• The extent to which PMR and GCA are associated requires further research to clarify the strength of this association • Findings suggest that PMR may not be as prevalent in patients prior to their GCA diagnosis, but is strongly associated

Clinical Feature	Systematic review findings		Findings from electronic health records	Conclusions & recommendations
	Prevalence	**Association**		
Weight loss/Anorexia	Moderate/low	Strong positive	• Low recorded prevalence • Strong positive association with a GCA diagnosis	• The findings from this thesis suggest there is an association between weight loss/anorexia and a diagnosis of GCA. • Few previous articles have investigated this possible association • Further research is required to quantify this relationship
Constitutional/systemic symptoms	High	Strong positive (non-statistically significant)	• Low recorded prevalence • Strong positive association with GCA diagnosis	• Health practitioners should monitor potential patients for these symptoms • A universal definition of constitutional symptoms is required
Fatigue	Moderate	Not enough data	• Low recorded prevalence • Strong association with GCA diagnosis	• The low prevalence of fatigue could be due to lack of Read code use for this symptom. • Health practitioners should be aware that there could be an association between fatigue and a GCA diagnosis • Further research is required
Fever	Moderate	Moderate positive (non-statistically significant)	• Low prevalence • Strong association with a diagnosis of GCA	• The coding of fever in primary care EHR should be improved as this could account for the low prevalence • Results imply there is an association between fever and a GCA diagnosis
Jaw Claudication/Jaw pain	Moderate/low	Strong positive	• No read code available for jaw claudication • Prevalence of jaw pain was low	• Further work is required to fully investigate the association between jaw claudication and a GCA diagnosis

			• Unable to quantify the association between jaw pain and a GCA diagnosis.	• With the introduction of SNOMED in UK primary care in 2018 there is now a code in primary care for jaw claudication, hence future research can include this as a clinical feature
Clinical Feature	**Systematic review findings**		**Findings from electronic health records**	**Conclusions & recommendations**
	Prevalence	**Association**		
Any visual impairment	Moderate	Negative (non-statistically significant, OR < 1)	• Very low recorded prevalence • Strongly associated with a GCA diagnosis	• Visual impairment remains associated with a GCA diagnosis • Prevalence may not be as high as has been previously reported
Abnormal temporal artery	Moderate	Strong positive (non-statistically significant)	• No Read code available.	• Abnormal temporal artery has been established as an indicator of GCA • A code that can be used in primary care to record this symptom should be developed. Possibly for inclusion in the SNOMED hierarchy
Arthralgia/Myalgia	Low	Moderate positive (non-statistically significant)	• Low prevalence • Strong association with a subsequent diagnosis of GCA	• Further work is required to quantify this relationship
Cardiovascular diseases	Moderate/low	Not enough data	• Low prevalence • Moderate positive association with a diagnosis of GCA	• Further work is required to quantify this relationship
Diabetes	Low	Not enough data	• Moderate prevalence • Strong association with a diagnosis of GCA	• Further work is required to quantify this relationship

Clinical Feature	Systematic review findings		Findings from electronic health records	Conclusions & recommendations
	Prevalence	**Association**		
Malaise Scalp tenderness Ischaemic optic neuropathy Peripheral arthritis Ophthalmic symptoms Ocular symptoms Anaemia Amaurosis Fugax Cough Psychological conditions Neurological conditions Limb claudication	Moderate/low	Not enough data	No Read code available	• Despite the low prevalence found in previous articles, further research may be required to quantify if these clinical features have any association with a diagnosis of GCA

8.2.3 Methodological findings

8.2.3.1 Primary care electronic health records

Primary care consultation data is a practical and useful resource for observational research in the UK, for studies that investigate health care utilisation and management, and for investigating clinical features that present prior to a diagnosis of GCA, or other similarly difficult to diagnose conditions. They contain patient information over a potentially long-period of time, in some instances decades, of consultations, prescriptions, test results, and referrals. This allows for both long prospective and retrospective follow-up. Retrospective follow-up is more practical in studies, like the ones completed in this thesis, that attempt to investigate which clinical features are associated or indicative of a subsequent diagnosis, in this case GCA. Overall, clinical features that are present prior to a GCA diagnosis should be recorded in the patient's primary care record. Hence, researchers can identify these clinical features via Read codes, record when they were coded into a patient's record, and quantify if there is an association between the clinical feature and the condition of interest. It is also possible to quantify this association over long periods of time, thereby including a longitudinal aspect to the research.

Over two decades of primary care records were available from CPRD for this study, including the two years prior to an eventual GCA diagnosis. This level of information would not be available in prospective cohort studies. Primary care records also do not rely on patient recall, thereby avoiding recall bias in the results. Limitations of using EHR's for this type of research are mainly around the coding of clinical features. EHR's are used for documentation and clinical use by clinicians delivering care and not specifically for research purposes and so certain limitations of their use have to be accepted. This thesis has found that not all clinical features of interest will have a corresponding code, and even if there is, it may not be used

frequently, if at all. Hence, there is a possibility of lack of recording for some important clinical features hypothesised to be associated with the condition of interest. Additionally while not coded, important information relevant to GCA may well have been recorded in the EHR, for example as free text, but owing to the nature of CPRD data, would not feature in our analysis and is a recognised limitation of this dataset and these methodologies.

Due to the possible long periods of retrospective follow-up in EHR's like CPRD, they have potential to be used in the future to identify presenting clinical features for conditions that are equally difficult to diagnose, such as Axial spondyloarthritis (AxSpa).

8.2.3.2 Coding in primary care

An area of difficulty in this thesis was the mapping of clinical features to Read codes. There were over 30 clinical features identified in the systematic review, but only 14 were available to be investigated via Read codes. Clinical features of interest, and that were suspected to be highly associated with GCA from previous studies, such as headache and visual impairment, were easily mapped to relevant Read codes. However, jaw claudication, a clinical feature thought to be associated with GCA, did not have a corresponding Read code. Other clinical features identified in the review, such as abnormal temporal artery, scalp tenderness, and limb claudication were other such features that a Read code could not be mapped to. In the UK, Read codes are, at the time of writing, being phased out in primary care, to be replaced by SNOMED codes. There is currently a SNOMED code for jaw claudication, meaning that future studies into GCA using primary care data could be able to include this clinical feature if it is used. Thirteen of the 14 clinical features were able to be mapped directly to a Read code, and these included the majority of the principal features

hypothesised to be associated with a diagnosis of GCA and that were identified in the review.

Connected to this is the accuracy of Read code use in primary care health records. It is not guaranteed that Read codes are always correctly used by healthcare professionals. This could be accidental, or could be related to the point raised previously, that not all conditions can be mapped to the Read code hierarchy. Therefore, other less appropriate codes for clinical features may be used instead, not recorded at all, or recorded purely in the free text. Free text is not available for research purposes in CPRD. The diagnosis of GCA has been validated in CPRD previously (Smeeth et al., 2006), and there is a limited selection of Read codes for this condition, hence it is not unreasonable to assume that the accuracy of GCA recoding in primary care is sufficient to be used for research.

A further aspect of coding which required careful consideration was in defining the prevalence of comorbidities, specifically those with a 'recorded' or 'treated' definition. This was undertaken because the prevalence of hypertension differed between recorded and treated definitions. Prevalence of hypertension was low when only Read codes were used to identify hypertensive patients. This prevalence improved when Read codes were used in conjunction with prescription information. This leads to the hypothesis that when defining comorbidities in EHR it may be more accurate to include prescriptions into the definition when feasible. The reasons for this low prevalence in comorbidities may be due to Read code use for chronic conditions. It may be the case that Read codes for chronic conditions are only used at initial diagnosis, and not subsequently added into a patient's record after this unless it is for a review, commonly conducted in patients with diabetes or hypertension. This has been shown to be an issue for CPRD (Jordan et al., 2007). Therefore, the most accurate way of identifying patients with chronic conditions or comorbidities is though

prescription information if there is medication always and exclusively used for these conditions, as these patients are likely to be on long-term medication which will be reflected in the patient's record.

8.2.3.3 Latent class analysis in primary care EHR

As detailed in Chapter 7 section 7.2, Latent Class Analysis (LCA) has been used in previous research to derive patterns of clinical features for AxSpa (Sepriano et al., 2020) to some success. This thesis aimed to use the same methodology applied to GCA, a condition that has proved difficult to promptly diagnose. The main difference between this thesis and the study by Sepriano et al (2020) was the use of primary care EHR. Sepriano et al (2020) used prospective cohorts for their study, with limited retrospective follow-up.

The length of follow-up and the content of primary care EHR's makes the application of LCA methodology in this setting useful for deriving patterns of presenting clinical features prior to the diagnosis of GCA, and similarly difficult to diagnose conditions. LCA methodology allows for comparison between latent classes based on age, gender, and any demographic variable that is available in primary care. Despite the problems around coding in primary care, as discussed in section 8.2.3.2, EHR's are still a large resource with information on all consultations and thereby the clinical features that a patient presents with prior to their GCA diagnosis. This retrospective follow-up can be over a long period of time, thereby allowing greater flexibility of how far back the patient's record is investigated. Overall, LCA methodology is a good tool for research investigating presenting clinical features prior to the diagnosis of a condition, such as GCA.

8.3 Definitions in electronic health records

8.3.1 GCA

A diagnosis of GCA in the UK is usually recorded in a patient's primary care record via the use of morbidity codes (Read codes in the timeframe of this study). Recommended clinical practice in primary care is to prescribe glucocorticoids to a patient with suspected GCA, and to refer them to a secondary care for confirmation of diagnosis (Mackie et al., 2020). Therefore a "true" diagnosis of GCA would include confirmation from a rheumatologist/specialist (which may include a positive temporal artery biopsy result of a GCA diagnosis) and then a Read code for GCA entered into the EHR. A diagnostic Read code should not ordinarily be added to the patient's record until confirmation has been received following referral to secondary or specialist care, i.e. only after confirmation has been received from secondary or specialist care should the Read code be added (Mackie et al., 2020). This could mean, in the case of patients found to have GCA, that the date of suspected diagnosis is the date of the first prescription of glucocorticoids, and the date of first Read code use is the confirmed diagnosis. The time between the two dates, given referral is meant to be urgent, should be small, and therefore have a negligible effect on the incidence estimates.

The definition of GCA employed in this thesis was that patients had to have a Read code for GCA, with a sensitivity analysis requiring one or more prescriptions of glucocorticoids within 6 months of diagnosis. There is a possibility that a small proportion of GCA patients included in this thesis, mainly those who had no or only one recorded prescription of glucocorticoids in the 6 months after diagnosis, did not actually have GCA. For these patients, this may mean that a Read code for GCA was added to the patient's record prior to referral. As aforementioned, good practice is to add a diagnostic Read code to a patient's record after

confirmation from secondary/specialist referral, and not before. However, the sensitivity analysis conducted shows that the incidence/prevalence of GCA, and the associations with individual clinical features did not differ significantly between GCA patients defined using a Read code only, and those who were required to have one or more prescriptions of glucocorticoids. Hence, the number of patients wrongly included as having GCA in this thesis should be low.

8.3.2 Clinical features

The definition of clinical features in this thesis required a coded record of the clinical feature in the patient's record prior to their diagnosis of GCA. A previous study has found that only 37% of the features discussed during a consultation are coded into the patient's record, and on average 2.5 problems are discussed per consultation (Salisbury et al., 2013). This could indicate that not all clinical features reported in a consultation are added to the patient's record. It is possible that the most indicative ones, in the case of GCA, headache, and visual complications, will be coded, over less recognised or non-specific features. It is also possible that multiple or the full list of presenting features will not be recorded or coded in the same consultation, and therefore from the coded EHR records it may appear as though a patient only had one clinical feature prior to their GCA diagnosis, when in reality they may have had multiple features. These may have been documented as free text.

The Read codes used in this thesis were based around the GCA literature, input from medical practitioners, and finding Read codes that are used in primary care to code these conditions. Via this method, the code lists used throughout this thesis should be comprehensive and appropriate. An acknowledged limitation of all EHR research is that analysis can only use what is coded and cannot impute what is not recorded or coded in a consultation. However,

it is likely that the most important clinical features, those which are the patient's main reason for consultation and potentially the ones the GP would use as indicative of possible GCA, would be coded in the patient's record, and therefore would be available to use for analysis.

8.4 Strengths & limitations of the thesis

8.4.1 Strengths

The main strength of this thesis is its setting within primary care. In the UK over 95% of the population is registered with a general practice (NHS, 2012). Primary care is where patient's first present with symptoms, and is where many conditions, including GCA, are first identified and managed (Helliwell et al., 2014). Details of a patient's demographics, symptoms, diagnosis, results from specialist referrals, and management of their condition will all be added to their record, which is available for practices that opt-in to CPRD. CPRD has been shown to be generally representative of the UK population based on age, gender, and ethnicity (Herrett et al., 2015), therefore the results from studies using this database are generalisable to the UK population. This is the biggest study of GCA in the UK, with the largest GCA sample taken from CPRD to be included in a study, with over 9,000 GCA cases used for analysis.

This thesis used two different definitions of GCA to identify cases to be included in analyses. The main method was using GCA Read codes, with the second including glucocorticoid prescriptions in conjunction with Read codes. A diagnosis of GCA using Read codes has been validated in a previous study (Smeeth et al., 2006). This thesis shows that similar associations and results are found whether diagnosis of GCA is via glucocorticoid prescription plus Read code, or Read code only. Through these different methods of identifying GCA cases to be

included in the analysis, this thesis has shown that the results found are robust to GCA case definition.

A further strength of this thesis is the novel approach to identifying and modelling clinical features prior to a diagnosis of GCA. A wide range of single or multi-centre studies investigating presenting clinical features were identified as part of the review conducted at the beginning of this thesis. Very few were conducted in the UK, and even fewer in primary care. All studies published prior to this work have considered clinical features as independent of each other, with their main aim being to investigate the relationship on a diagnosis of GCA, independent of other conditions or symptoms. However, this is not likely to be the usual case in older patients seen in primary care who commonly experience multimorbidity. Therefore, the latent class analysis methodology conducted as a part of this thesis is a novel approach in the research of GCA and attempted to identify classes of clinical features that would help GPs to identify possible GCA. To my knowledge, no previous study has taken a similar methodological approach. Therefore, this analysis and the results derived from it are novel, and the methods should be pursued for further research into GCA.

8.4.2 Limitations

One limitation was that several variables were not available to be included across several aspects of this thesis. Patient demographics such as age, gender, BMI, and lifestyle habits were available to be included in the analysis. However, variables such as family history are not available in CPRD. Currently there are few articles investigating the relationship of family history on a diagnosis of GCA, and this would be an interesting area of future research. A further confounding variable that was not included in this analysis, was a general variable to represent overall patient morbidity, such as the Charlson Comorbidity Index (CCI). The CCI is

a score that predicts mortality, by taking the number of comorbidities a patient has and creating an overall score (Hall, Ramachandran, Narayan, Jani, & Vijayakumar, 2004). Including this score in an analysis would have allowed the examination of whether GCA patients are generally frailer than non-GCA patients, or if there is an association between selected comorbidities, like those included in this thesis, and whether GCA is associated to patient fragility. However, there is evidence that individual comorbidities are a better measure in some instances (Austin, Wong, Uzzo, Beck, & Egleston, 2015) and the CCI was also developed in secondary care, and therefore has not been validated for use in a primary care setting (Crooks, West, & Card, 2015).

8.5 Implications for clinical practice

GCA remains a challenging condition to diagnose due to the wide range of presenting clinical features, some of which are indicative of other more prevalent conditions. Though headache remains one of the most common and strongly associated symptoms and trigger for suspecting and subsequent diagnosis of GCA, this thesis has shown that there are several other features that should be considered, independently or in conjunction with a headache, such as treated hypertension, and PMR or associated PMR type symptoms at presentation. Headache has been established as a strong feature of GCA in people over 50 years, and is included in current guidelines concerning the diagnosis of GCA (Mackie et al., 2020; NICE CKS, 2020). It is also the symptom that GPs associate with and trigger a suspicion of potential GCA (Helliwell et al., 2018). The results of this thesis have supported this, with headache being highly prevalent and strongly associated with a diagnosis of GCA, and a predominant feature in each class of presenting features. The focus for guidelines should begin to highlight that headache, whilst associated, is not a definitive sign that a patient has GCA, and

that there may be other signs and symptoms, in conjunction with a headache, that may also indicate that the patient has GCA, such as elevated ESR. Headache, on its own, is not a conclusive sign that a patient has GCA, and other clinical features should also be taken into consideration before a patient is referred for specialist review to confirm diagnosis.

Hypertension was found to be strongly associated with a diagnosis of GCA and was a dominant feature in two of the five classes. Although research into the relationship between hypertension and incident GCA is limited and has produced varying results, it is certainly worth exploring if hypertension is a risk factor or an indicator of GCA and presents a potential future area of research. The type of hypertension, whether it is new onset hypertension in the elderly that is more associated with incident GCA, or a worsening or loss of control of previously stable long-standing hypertension needs to be considered. This could also indicate that there is a spectrum of severity for GCA. A patient may have constitutional symptoms, secondary hypertension, and persistent raised inflammatory markers, and not be recognised as having GCA due to not presenting with traditional GCA-associated symptoms like visual disturbances or headache, and hence remain undiagnosed for a longer period of time.

Comorbidities had a longer time from recorded onset to GCA diagnosis, even within the 2 years prior to eventual GCA diagnosis. PMR was the comorbidity with the shortest time at 6/7 months. This could suggest that where symptoms are indicators of a subsequent GCA diagnosis (presenting symptoms), some comorbidities may be risk factors for GCA, and this may not be exclusive to PMR.

This thesis has found that although some clinical features, such as fever, weight loss, and visual impairment, may have low recorded prevalence, they are still associated with a GCA diagnosis. Low recorded prevalence could be due to coding, in that these conditions may not

be widely coded in a consultation. This finding implies that GPs should be aware that there are clinical features more than just a headache that are associated with a GCA diagnosis and take the time to inquire about further symptoms or features that a patient may not have mentioned in the consultation.

8.6 Future areas for research

There remain other potential presenting clinical features for GCA in primary care. Many previous studies have focused on presenting symptoms prior to a diagnosis (E. Machado et al., 1988; Myklebust et al., 1996; Petri et al., 2015). However, areas for future research should broaden to include comorbidities other than PMR, and clinical features not evaluated in this thesis. This thesis has shown a positive association between treated hypertension, cardiovascular conditions, and diabetes on a subsequent diagnosis of GCA. However, the results from the systematic review show that there are few published articles in which these have been investigated. It is possible that there are more comorbidities that are associated with GCA other than PMR (general cardiovascular conditions other than hypertension), and future research should take steps into identifying these.

This thesis included information on GCA patient demographics, such as gender, age at diagnosis, BMI, smoking status, alcohol consumption, and for patients in England their IMD 2015 score. A variable not included in this analysis was patient ethnicity as there is a lack of completeness in primary care records. There are few published studies that have investigated the association between ethnicity and GCA, with varying results (Gruener et al., 2019; Pereira et al., 2011). It is generally thought that GCA in populations other than Caucasian is rare (Weyand & Goronzy, 2014). However, the study conducted by Gruener et al (2019) found that there was no difference in GCA incidence between white and black

patients. Another study (Pereira et al., 2011) investigated GCA in Asian patients, and found that the incidence was lower for those of Asian descent compared to Caucasians. A limitation of this study was the small sample size of Asian patients included in the analysis, which caused large variability of the estimates, and should therefore not be viewed as a firm conclusion. Further research into GCA should include information on ethnicity, and investigate the association, if one exists, between race and a diagnosis of GCA. Another variable not included in this thesis was family medical history, as this is not available in EHR. The role of genetics in GCA has been investigated (David Carmona, Gonzá Lez-Gay, & Martín, 2014), but the role of family history has yet to be widely investigated beyond small case reports (Fietta, Manganelli, Zanetti, & Neri, 2002).

The next steps for GCA research may be in predictive modelling or machine learning. GCA remains a difficult condition to recognise in primary care, with varying presenting symptoms and potentially long time-periods from symptom onset to diagnosis. It could be that a patient consults with a fever up to 12 months prior to their GCA diagnosis, and then 6 months prior weight loss/anorexia, and then 1 months prior a headache. It is difficult over a length of time like this for a GP to connect all of these symptoms to GCA. Hence, future research should focus on creating an algorithm that could be implemented in general practices that would flag or alert the GP to the potential presence of GCA based on a patient's previous consultations and the build-up of potential indicators and give a recommendation on whether it is suitable to refer the patient for further diagnosis. To create a predictive algorithm, machine learning techniques, such as decision trees, could be used. A decision tree is a machine learning methodology that can be used, similarly to LCA, to classify data into classes based on their responses to observed variables, and therefore can be used to predict which class a new patient would be in (Lantz, 2013). The decision tree

creates new decision rules (which patient goes in which class) based on the data it is given. The benefits of decision trees is that they are more transparent than other machine learning techniques as the tree produced by the analysis shows the probability it used to classify each point of data (i.e. a patient), and both categorical and continuous data can be used (Handelman et al., 2018). Their visual representation also makes them easier to understand by a lay audience. This methodology could be a starting point for developing an algorithm that could be used to flag GCA patients in primary care, so they are diagnosed more promptly.

Future research could also examine the generalisability of the classes produced in this thesis, attempting validation of these in other data. Although CPRD is generalisable to the UK population, it cannot be assumed that the classes from the LCA analysis are. This is an area of future research, to conduct similar analysis in other databases or sets of data, not necessarily EHR, and see if they produce the same classes of presenting features.

A general area which future research could expand upon is the use of LCA for identifying common patterns of presenting clinical features prior to a diagnosis of a specified condition, such as that conducted in this thesis. LCA has advantages over other clustering methodologies, and a wide range of comparisons can be made between classes, and even within classes, such as age, gender, general indicators of health, and the number of times a patient presented with a clinical feature. Models can be assessed via a range of model and class fit statistics, and software to conduct this analysis is widely available. The researcher has total control over what variables are included in the models and can also choose the most clinically and/or statistically relevant model. Classes can also be tested on more than one dataset to quantify their generalisability to a different population. There is also the potential in future research to assess if different patterns are found based on age, gender,

and ethnicity. A final area of research for future consideration is to expand the use of LCA by extending to more complex methods that better incorporate the longitudinal aspect of EHR's, such as Latent Class Growth Analysis (LCGA). The use of LCGA would be able to quantify if the patterns of presenting clinical features differed depending on how long prior to a GCA diagnosis they were presented with (Strauss, Jones, Kadam, & Jordan, 2014).

8.7 Conclusions

This thesis provides updated incidence and prevalence estimates for GCA in the UK population and presents an extensive examination of the prevalence and association of individual clinical features with a subsequent diagnosis of GCA, and patterns of clinical features linked to GCA. From this body of work, it remains clear that GCA is a difficult condition to recognise in primary care, with a spectrum of clinical features experienced. However, this work does confirm the continued importance of headache, elevated ESR, and PMR as indicators of a GCA diagnosis, but importantly highlights hypertension as a commonly experienced and strongly associated clinical feature with a subsequent diagnosis of GCA, and therefore warrants further investigation. This thesis has also shown the importance of investigating combinations of clinical features rather than just individual features that occur prior to a diagnosis of GCA.

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Appendix 3.1 – Systematic review protocol

Arthritis Research UK Primary Care Centre

Systematic Review Protocol & Support Template

This template is primarily intended to help you plan your review in a systematic way. A copy of this completed form will be available via the intranet to help others carrying out reviews in the future and to avoid duplicating work already undertaken in the Centre. Keeping a record of all the reviews will also assist in planning the work of the Centre and ensuring adequate methodological support. Not all the information will be relevant to every review and items should be adapted to fit the type of review that is being undertaken.

The template has been updated to include all the items from the PRISMA-P checklist (http://www.prisma-statement.org/Extensions/Protocols.aspx). All systematic reviews should be registered with PROSPERO database (http://www.crd.york.ac.uk/PROSPERO/) unless the review is methodological.

Title of the review	The risk associated with symptoms and comorbidities in patients before diagnosis of giant cell arteritis
First reviewer	Lauren Barnett
Other reviewers (with role/contribution in the review)	Chris Morton (second reviewer).
Clinical Portfolio Group	Inflammatory
Funding source	ACORN

PROSPERO registration number	TBC

Amendments to the protocol	N/A

1. Background to review

Giant cell arteritis (GCA) is the most common form of large vessel vasculitis, which affects approximately 10 in 10,000 people in the UK (Petri et al., 2015). There has been relatively little research investigating the clinical features (symptoms, comorbidities or medical abnormalities) which occur before a GCA diagnosis. There is currently a delay in diagnosis (an average of 9 weeks, longer if no cranial symptoms are present (Prior et al., 2017)) between first presentation of symptoms and final GCA diagnosis. Therefore, understanding the most common clinical features patients present with before diagnosis, may aid mechanism of diagnosis and reduce delay.

Clinical features include symptoms (such as headache, jaw claudication, and visual disturbances) (Smetana & Shmerling, 2002), comorbidities (such as cardiovascular disease, and polymyalgia rheumatica) (González-Gay & Pina, 2015) or medical anomalies (such as elevated erythrocyte sedimentation rate (ESR) which positive temporal artery biopsy) present before a diagnosis of GCA (Salvarani et al., 2005).

From previous literature, and the American College of Rheumatology's 2010 diagnosis criteria on GCA, headache is a common symptom of GCA (Gene G. Hunder et al., 1990). However studies have found that 24% of patients do not experience this symptom (Hassan et al., 2011). Visual complications usually tend to be a warning sign of impending GCA diagnosis, and complete visual loss occurs in 15-20% of patients (Salvarani et al., 2005). Tongue or jaw claudication has been observed in GCA patients, and usually is a risk factor for future ischaemic complications (Smetana & Shmerling, 2002). Other literature has found that cerebrovascular accidents (strokes), and hypertension have also

been noted as symptoms pre-diagnosis (Mackie et al., 2011). Due to GCA being more common in patients older than 70 years old it has proven difficult to know if the aforementioned symptoms are linked to GCA.

There are also many comorbidities linked with GCA. PMR can also be a comorbidity, with between 40% and 60% of GCA patients developing PMR (González-Gay & Pina, 2015). Patients with GCA have an increased risk of cardiovascular disease, osteoporosis, and severe infections such as septicaemia compared to non-GCA patients (Mohammad, Nilsson, Jacobsson, Merkel, & Turesson, 2015). Vision complications, such as blurred vision and diplopia, can also continue after diagnosis, but can usually be remedied after steroid treatment has commenced, however if complete vision loss has occurred then this is usually irreversible (Petri et al., 2015). Due to the seriousness of the complications associated with untreated and unrecognised GCA it is imperative that symptoms are diagnosed early.

The overall aim of this project is to search the literature to determine the risk of developing certain clinical features in patients prior to their GCA diagnosis.

2. Specific objectives/questions the review will address

- To Identify the risk of patients with GCA developing certain clinical features (symptoms, comorbidities, etc.) prior to GCA diagnosis

3. a) Eligibility Criteria for including studies in the review If the PICOS format does not fit the research question of interest, please split up the question into separate concepts and put one under each heading	
i. Population, or participants and conditions of interest	Patients diagnosed with GCA diagnosed in a medically recognised way, i.e. by health care professional, or by biopsy.
ii. Interventions/Exposure/item of interest	N/A
iii. Comparisons or control groups, if any	Controls or comparison groups must not have a previous diagnosis of GCA.
iv. Outcomes of interest	Since this review is looking at clinical features pre-diagnosis, outcomes of interest encompass symptoms, comorbidities etc. that have been recorded prior to a diagnosis of GCA.
v. Setting	Primary and/or Secondary care.
vi. Study designs	All quantitative study designs.

3. b) Criteria for excluding studies not covered in inclusion criteria Any specific populations excluded, date range, language, whether abstracts or full text available, etc
• Those with a population of <18 year olds • There will be no restriction on language, but those which can't be translated won't be included in the final paper

4. Search methods	
Electronic databases & websites Please list all databases that are to be searched and include the interface (eg NHS HDAS, EBSCO, OVID etc) and date ranges searched for each. **NB All search strategies should be reviewed by Jo Jordan or Nadia Corp BEFORE searching begins**	MEDLINE: inception to date. (OVID) EMBASE: inception to date (OVID) CiNAHL: inception to date (EBSCO) Web of Science: inception to date
Other methods used for identifying relevant research ie contacting experts and reference checking, citation tracking	Reference list searching of selected papers after full text stage. Checking for papers by key researchers in the field Ask experts in the field

Journals hand searched If any are to be hand searched, please list which journals and date searched from, including a rationale.	N/A

5. Methods of review	
How will search results be managed & documented? ie which reference management software, how duplicates dealt with	All search results will be exported into Mendeley, which has the ability to remove duplicates from lists of imported references.
Selection process Number of reviewers, how agreements to be reached and disagreements dealt with, etc.	LB will complete the main screening and selection process (titles and abstracts), whilst another reviewer (Chris Morton, PhD student) will serve as the second reviewer to screen abstracts only. All disagreements will be settled by consensus, with LB's lead supervisors arbitrating if a consensus cannot be reached. Alyshah Abdul-Sultan and James Prior will check a proportion of the papers for suitability.

Quality assessment Tools or checklists used with references or URLs, was this piloted? Is it to be carried out at same time as data extraction?	Newcastle-Ottowa scale.
How is data to be extracted? What information is to be collected on each included study? If databases or forms on Word or Excel are used, were these piloted and how is this recorded and by how many reviewers?	Extracted data will be collated into an Excel file to compare study attributes. A draft table can be found in appendix A.

Outcomes to be extracted & hierarchy/priority of measures ie which measure is preferred and if that is not available which is next in order of preference?	The outcomes to be extracted are GCA diagnosis, and clinical features pre-diagnosis. Please find a data extraction table in the appendix of this document. Collected attributes are: Clinical features pre-diagnosis Defined outcome (GCA diagnosis) Population demographics, such as age, sex, sample size, etc. Comorbidities recorded Time to GCA diagnosis Quantitative measure of risk of GCA, such as a risk ratio.
Narrative synthesis Details of what methods, how synthesis will be done and by whom. Is the Narrative Synthesis Framework to be used?	Suitable articles will be compared by LB using narrative synthesis, comparing characteristics of included studies in tables.

Meta-analysis Details of what and how analysis and testing will be done. If no meta-analysis is to be conducted, please give reason.	A meta-analysis will be undertaken if sufficient data can be extracted.
Will the overall strength of evidence be assessed? If so, how? ie GRADE?	This review is not attempting to answer a clinical question, therefore the grading of evidence isn't thought to be necessary.

6. Presentation of results	
Outputs from review Papers and target journals, conference presentations, reports, etc	The main output of this systematic review is a chapter of the PhD thesis, and a secondary output is to publish a paper in a peer-reviewed journal.

7. Timeline for review – when do you aim to complete each stage of the review	
Protocol	November
Literature searching	December/January
Quality appraisal	February

Data extraction	March
Synthesis	May
Writing up	July/August

Support – please state if advice/training or personnel required at each stage	
SR overview	None
Protocol development	Advice needed.
Literature searching	Charles Hay to help with search strategy and database searching.
Quality appraisal	None.
Data Extraction	None.
Synthesis	None
Writing up	None

Appendix 3.2 – Systematic review search strategy

Systematic review strategy

MEDLINE (OVID): inception (1946) to 04/12/2017 (produced 4139 articles)

1. Exp Giant cell arteritis/
2. Giant adj cell adj (arteritis or aoritis or aortitides).ti,ab.
3. Cranial adj (arteritis or arteritides).ti,ab.
4. “Horton$ disease”.ti,ab.
5. Temporal adj (arteritis or arteritides).ti,ab.
6. Aortic arteritis.ti,ab.
7. Large vessel vasculitis.ti,ab.
8. Or/1-7
9. Symptom$1.ti,ab.
10. Manifestation$1.ti,ab.
11. Comorbid$.ti,ab.
12. (Clinical adj (features or attributes or characteristics)).ti,ab.
13. Exp Polymyalgia rheumatica/
14. “Polymyalgia rheumatica”.ti,ab
15. Visual disturbances”.ti,ab.
16. Diplopia.ti,ab.
17. “Double vision”.ti,ab.
18. “Visual loss”.ti,ab.
19. “Blindness”.ti,ab
20. “Partial visual loss”.ti,ab.
21. “Total visual loss”.ti,ab.
22. “Transient visual loss”.ti,ab.
23. “Permanent visual loss”.ti,ab.
24. Exp cataract/
25. Cataract.ti,ab.
26. “Blurred vision”.ti,ab.
27. “Chest infection”.ti,ab.
28. Exp Cystitis/
29. Cystitis.ti,ab.
30. “Severe infections”.ti,ab.
31. Septicaemia.ti,ab.
32. Exp Urinary tract infections/
33. “Urinary tract infection”.ti,ab.
34. “Cranial symptoms”.ti,ab.
35. Headache.ti,ab.
36. “Temporal headache”.ti,ab.
37. “Abnormal temporal arter$”.ti,ab.
38. “Scalp tenderness”.ti,ab.

39. “Jaw claudication”.ti,ab.
40. “Tongue claudication”.ti,ab.
41. “Weight loss”.ti,ab.
42. Exp Fever/
43. Fever.ti, ab.
44. “Erythrocyte sedimentation rate”.ti, ab.
45. “Isch?mic heart disease”.ti,ab.
46. Exp stroke/
47. Stroke.ti,ab.
48. “Cerebrovascular accident”.ti,ab.
49. Exp Hypertension/
50. hypertension.ti,ab.
51. “Isch?mic complications”.ti,ab.
52. Exp Atherosclerosis/
53. atherosclerosis .ti, ab.
54. Exp Aortic aneurysm/
55. “Aortic aneurysm”.ti,ab.
56. Exp Diabetes mellitus/
57. “Diabetes mellitus”.ti,ab.
58. Exp osteoporosis/
59. Osteoporosis.ti,ab.
60. “Venous thromboembolism”.ti,ab.
61. Exp thyroid diseases/
62. “Thyroid disease”.ti,ab.
63. Falls.ti,ab.
64. Asthenia.ti,ab.
65. “Facial pain”.ti,ab.
66. Exp Musculoskeletal pain/
67. “Musculoskeletal conditions”.ti,ab.
68. “Back pain”.ti,ab.
69. “Neck pain”.ti,ab.
70. “Shoulder pain”.ti,ab.
71. Or/9-70
72. 8 AND 71
73. Limit 72 to humans

EMBASE via Ovid, inception (1974) to <insert current date> (scoping on 16/11/2017 produced 3994 articles)

1. Exp Giant cell arteritis/
2. Giant adj cell adj (arteritis or aoritis or aortitides).ti,ab.
3. Cranial adj (arteritis or arteritides).ti,ab.

4. “Horton$ disease”.ti,ab.
5. Temporal adj (arteritis or arteritides).ti,ab.
6. “Aortic arteritis”.ti,ab.
7. “Large vessel vasculitis”.ti,ab.
8. Or/1-7
9. Symptom$1.ti,ab.
10. Manifestation$1.ti,ab.
11. Comorbid$.ti,ab.
12. (Clinical adj (features or attributes or characteristics)).ti,ab.
13. Exp Polymyalgia rheumatica/
14. “Polymyalgia rheumatica”.ti,ab
15. “Visual disturbances”.ti,ab.
16. Diplopia.ti,ab.
17. “Double vision”.ti,ab.
18. “Visual loss”.ti,ab.
19. “Blindness”.ti,ab
20. “Partial visual loss”.ti,ab.
21. “Total visual loss”.ti,ab.
22. “Transient visual loss”.ti,ab.
23. “Permanent visual loss”.ti,ab.
24. Exp cataract/
25. Cataract.ti,ab.
26. “Blurred vision”.ti,ab.
27. “Chest infection”.ti,ab.
28. Exp Cystitis/
29. Cystitis.ti,ab.
30. “Severe infections”.ti,ab.
31. Septicaemia.ti,ab.
32. Exp Urinary tract infections/
33. “Urinary tract infection”.ti,ab.
34. “Cranial symptoms”.ti,ab.
35. Headache.ti,ab.
36. “Temporal headache”.ti,ab.
37. “Abnormal temporal arter$”.ti,ab.
38. “Scalp tenderness”.ti,ab.
39. “Jaw claudication”.ti,ab.
40. “Tongue claudication”.ti,ab.
41. “Weight loss”.ti,ab.
42. Exp Fever/
43. Fever.ti, ab.
44. “Erythrocyte sedimentation rate”.ti,ab.
45. “Isch?mic heart disease”.ti,ab.
46. Exp stroke/
47. Stroke.ti,ab.

48. “Cerebrovascular accident”.ti,ab.
49. Exp Hypertension/
50. hypertension.ti,ab.
51. “Isch?mic complications”.ti,ab.
52. Exp Atherosclerosis/
53. atherosclerosis .ti, ab.
54. Exp Aortic aneurysm/
55. “Aortic aneurysm”.ti,ab.
56. Exp Diabetes mellitus/
57. “Diabetes mellitus”.ti,ab.
58. Osteoporosis.ti,ab.
59. “Venous thromboembolism”.ti,ab.
60. Exp thyroid diseases/
61. “Thyroid disease”.ti,ab.
62. Falls.ti,ab.
63. Asthenia.ti,ab.
64. “Facial pain”.ti,ab.
65. Exp Musculoskeletal pain/
66. “Musculoskeletal conditions”.ti,ab.
67. “Back pain”.ti,ab.
68. “Neck pain”.ti,ab.
69. “Shoulder pain”.ti,ab.
70. Or/9-69
71. 8 AND 70
72. Limit 71 to humans
73. Limit 72 to Embase

CINAHL plus via EBSCO: inception (1986) to <insert date> (scoping on 04/12/2017 found 504, but only 142 after limiting to humans)

1. MH (“Giant cell arteritis”)
2. TI “Giant cell arteritis” OR AB “giant cell arteritis”
3. AB “Giant cell aoritis” OR AB “giant cell aortitides” OR AB “cranial arteritis” OR AB “cranial arteritides”
4. TI “Horton# disease” OR AB “Horton# disease”
5. TI “temporal arteritis” OR AB “temporal arteritis”
6. AB “Temporal arteritides” OR AB “aortic arteritis” OR TI “large vessel vasculitis” OR AB “large vessel vasculitis”
7. Or/1-6
8. TI Symptom# OR AB symptom#
9. TI Manifestation# OR AB manifestation#
10. TI Comorbid# OR AB comorbid#

11. TI “Clinical features” OR AB “clinical features”
12. TI “Clinical attributes” OR Ab “clinical attributes”
13. TI “Clinical characteristics” OR AB “clinical characteristics”
14. MH “polymyalgia rheumatica”
15. TI “polymyalgia rheumatica” OR AB “polymyalgia rheumatica”
16. TI “visual disturbances” OR AB “visual disturbances”
17. TI “diplopia” OR AB “diplopia”
18. TI “double vision” OR AB “double vision”
19. TI “blindness” OR AB “blindness”
20. TI “partial visual loss” OR AB “partial visual loss
21. TI “total visual loss” OR AB “total visual loss”
22. TI “transient visual loss” OR AB “transient visual loss”
23. TI “permanent visual loss” or AB “permanent visual loss”
24. MH “Cataract”
25. TI cataract or AB cataract
26. TI “blurred vision” OR AB “blurred vision”
27. TI “chest infection” or AB "chest infection"
28. MH “Cystitis+”
29. TI Cystitis OR AB cystitis
30. TI “severe infections” OR AB "severe infections"
31. TI septicaemia or AB septicaemia
32. MH “Urinary Tract Infections+”
33. TI “urinary tract infection” Or AB “urinary tract infection”
34. TI “cranial symptoms” OR AB "cranial symptoms"
35. TI headache or AB headache
36. TI “temporal headache” OR AB “temporal headache”
37. TI “abnormal temporal arter#” OR AB “abnormal temporal arter#”
38. TI “scalp tenderness” OR AB “scalp tenderness”
39. TI “jaw claudication” OR AB “jaw claudication”
40. TI “tongue claudication” OR AB “tongue claudication” OR TI “weight loss” OR AB “weight loss”
41. MH “Fever+”
42. TI fever OR AB fever
43. TI “Erythrocyte sedimentation rate” OR AB “Erythrocyte sedimentation rate”
44. TI “Isch?mic heart disease” OR AB “Isch?mic heart disease”
45. MH “Stroke+”
46. TI “stroke” OR AB “stroke”
47. TI “cerebrovascular accident” OR AB “cerebrovascular accident”
48. MH “Hypertension+”
49. TI hypertension OR AB hypertension
50. TI “Isch?mic complications” or AB “Isch?mic complications”
51. MH “Atherosclerosis”
52. TI “atherosclerosis” or AB “atherosclerosis”
53. MH “Aortic aneurysm+”

54. TI “aortic aneurysm” OR AB “aortic aneurysm”
55. MH “Diabetes mellitus+”
56. TI “diabetes mellitus” OR AB “diabetes mellitus”
57. TI Osteoporosis OR AB Osteoporosis
58. TI “Venous thromboembolism” OR AB “Venous thromboembolism”
59. MH “Thyroid diseases+”
60. TI “Thyroid disease” OR AB “Thyroid disease”
61. TI Falls OR AB Falls
62. TI Asthenia OR AB Asthenia
63. TI “Facial pain” OR AB “Facial pain”
64. TI “musculoskeletal conditions” OR AB "musculoskeletal conditions"
65. TI “back pain” OR AB “back pain”
66. TI “neck pain” OR AB “neck pain”
67. TI “shoulder pain” OR AB “shoulder pain”
68. Or/8-67
69. 7 AND 68
70. Limit 69 to humans

Web of Science: inception (1950) to 04/12/2017 (gave 1917 articles)

1. TITLE “giant cell arteritis” OR TOPIC “giant cell arteritis”
2. TITLE “giant cell aoritis” OR TOPIC “giant cell aoritis” OR TITLE “giant cell aortitides” OR TOPIC “giant cell aortitides
3. TITLE “cranial arteritis” OR TOPIC “cranial arteritides”
4. TITLE “Horton* disease” OR TOPIC “Horton* disease”
5. TITLE “temporal arteritis” OR TOPIC “temporal arteritis” OR TITLE “temporal arteritides” OR TOPIC “temporal arteritides”
6. TITLE “aortic arteritis” OR TOPIC “aortic arteritis”
7. TITLE “large vessel vasculitis” OR TOPIC “large vessel vasculitis”
8. TITLE “symptom*” OR TOPIC “symptom*”
9. TITLE “manifestation*” OR TOPIC “manifestation*”
10. TITLE “comorbid*” OR TOPIC “comorbid*”
11. TITLE “clinical features” or TOPIC “clinical features”
12. TITLE “clinical attributes” OR TOPIC “clinical attributes”
13. TITLE “clinical characteristics” OR TOPIC “clinical characteristics”
14. TITLE “Polymyalgia rheumatica” OR TOPIC “polymyalgia rheumatica”
15. TITLE “visual disturbances” OR TOPIC “visual disturbances”
16. TITLE “diplopia” OR TOPIC “diplopia”
17. TITLE “double vision” OR TOPIC “double vision”
18. TITLE “visual loss” OR TOPIC “visual loss”
19. TITLE “blindness” OR TOPIC “blindness”
20. TITLE “partial visual loss” OR TOPIC “partial visual loss”
21. TITLE “total visual loss” OR TOPIC “total visual loss”

22. TITLE “transient visual loss” OR TOPIC “transient visual loss”
23. TITLE “permanent visual loss” OR TOPIC “permanent visual loss”
24. TITLE “cataract” OR TOPIC “cataract”
25. TITLE “blurred vision” OR TOPIC “blurred vision”
26. TITLE “chest infection” OR TOPIC “chest infection”
27. TITLE “cystitis” OR TOPIC “cystitis”
28. TITLE “severe infections” OR TOPIC “severe infections”
29. TITLE “septic?mia” OR TOPIC “septic?mia”
30. TITLE “urinary tract infection*” OR TOPIC “urinary tract infection*”
31. TITLE “cranial symptoms” OR TOPIC “cranial symptoms”
32. TITLE headache OR TOPIC headache
33. TITLE “temporal headache” OR TOPIC “temporal headache”
34. TITLE “abnormal temporal arter*” OR TOPIC “abnormal temporal arter*”
35. TITLE “scalp tenderness” OR TOPIC “scalp tenderness”
36. TITLE “jaw claudication” OR TOPIC “jaw claudication”
37. TITLE “tongue claudication” OR TOPIC “tongue claudication”
38. TITLE “weight loss” OR TOPIC “weight loss”
39. TITLE “fever” OR TOPIC “fever”
40. TITLE “Erythrocyte sedimentation rate” OR TOPIC “Erythrocyte sedimentation rate”
41. TITLE “isch?mic heart disease” OR TOPIC “isch?mic heart disease”
42. TITLE “stroke” OR TOPIC “stroke”
43. TITLE “cerebrovascular accident” OR TOPIC “cerebrovascular accident”
44. TITLE “hypertension” OR TOPIC “hypertension”
45. TITLE “isch?mic complications” OR TOPIC “isch?mic complications”
46. TITLE “atherosclerosis” OR TOPIC “atherosclerosis”
47. TITLE “aortic aneurysm” OR TOPIC “aortic aneurysm”
48. TITLE “diabetes mellitus” OR TOPIC “diabetes mellitus”
49. TITLE “osteoporosis” OR TOPIC “osteoporosis”
50. TITLE “venous thromboembolism” OR TOPIC “venous thromboembolism”
51. TITLE “thyroid disease” OR TOPIC “thyroid disease”
52. TITLE “falls” OR TOPIC “falls”
53. TITLE “asthenia” OR TOPIC “asthenia”
54. TITLE “facial pain” OR TOPIC “facial pain”
55. TITLE “musculoskeletal conditions” OR TOPIC “musculoskeletal conditions”
56. TITLE “back pain” OR TOPIC “back pain”
57. TITLE “neck pain” OR TOPIC “neck pain”
58. TITLE “shoulder pain” OR TOPIC “shoulder pain”
59. Or/1-7
60. Or/8-58
61. 59 AND 60
62. Exclude MEDline

Appendix 3.3 – Systematic review data extraction form

Table 1: Data extraction form used for each article included in the review.

	Notes
First author surname	
Year of publication	
Study design	
Country	Country where the article was conducted
Quality	From the Newcastle-Ottowa scale
Healthcare setting	Primary, secondary, etc.
GCA population	How many GCA cases included in the article
GCA diagnosis	Type of diagnostic method used
Point of recording	Point at which clinical features were recorded
Samping period	
Sample size	
Patient gender (%F)	
Mean age (years)	
Age range (years)	
Clinical features included	
N/ Prevalence	
Clinical feature	Only filled in with respect to risk estimate
Unadjusted risk estimate	
95% CI	

Appendix 3.4 – Forest plots for prevalence meta-analysis

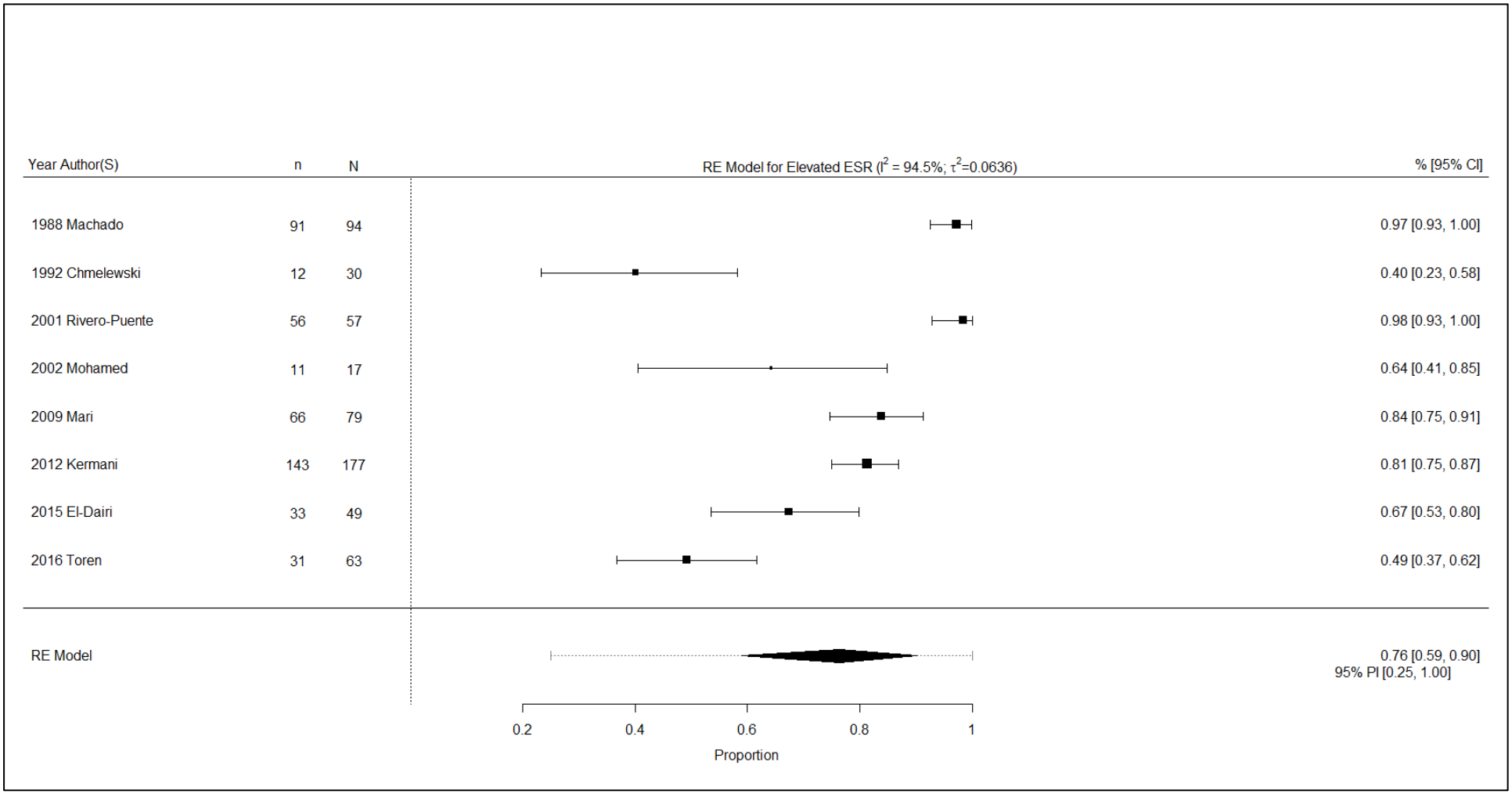

Figure 1: Meta-analysis forest plot for the prevalence of elevated ESR, showing raw prevalence data, study proportion, 95% CI, and 95% PI.

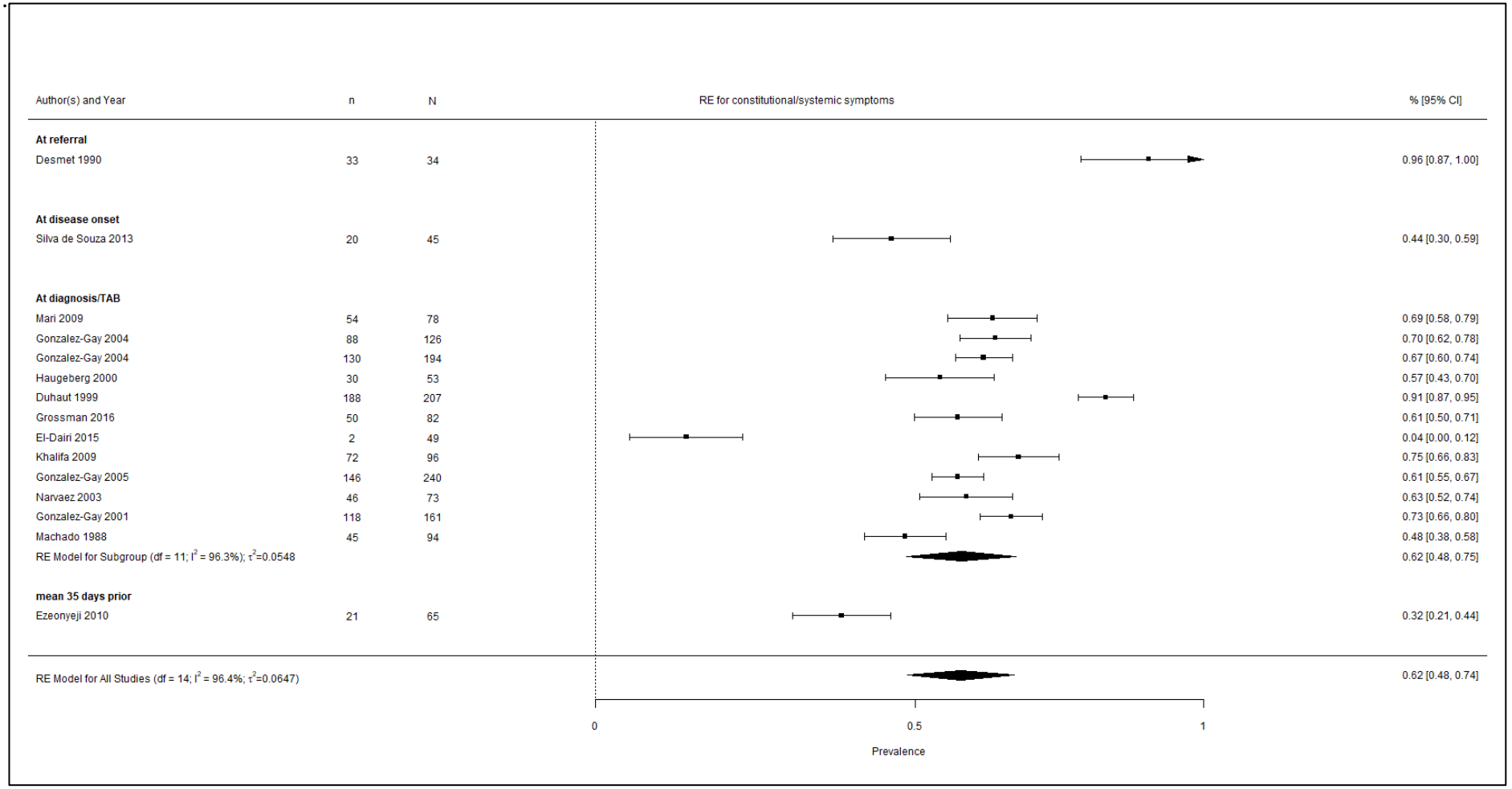

Figure 2: Meta-analysis forest plot for the prevalence of constitutional/systemic symptoms stratified by point of recording, showing raw

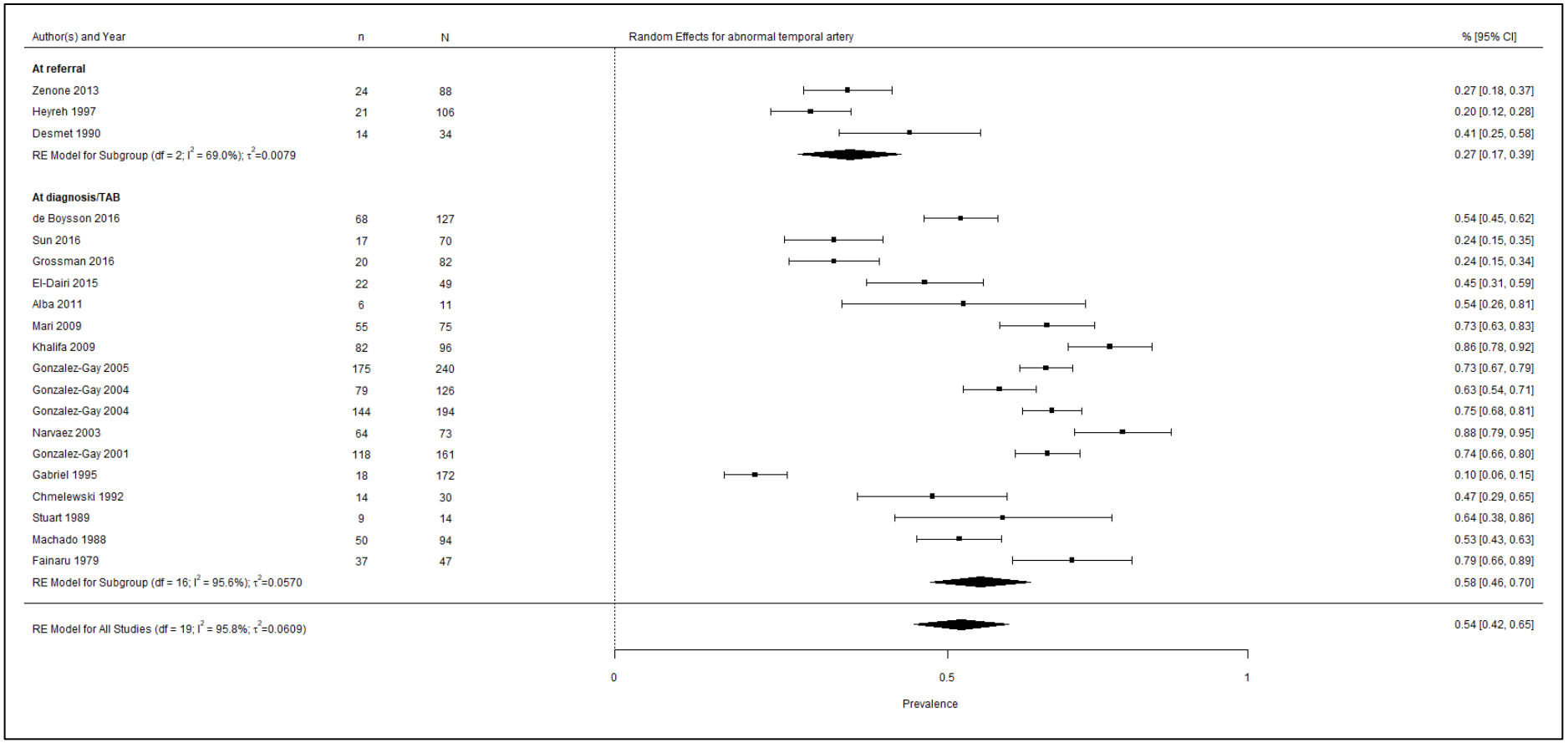

Figure 3: Meta-analysis forest plot for abnormal temporal artery stratified by point of recording, showing raw prevalence data, and 95%

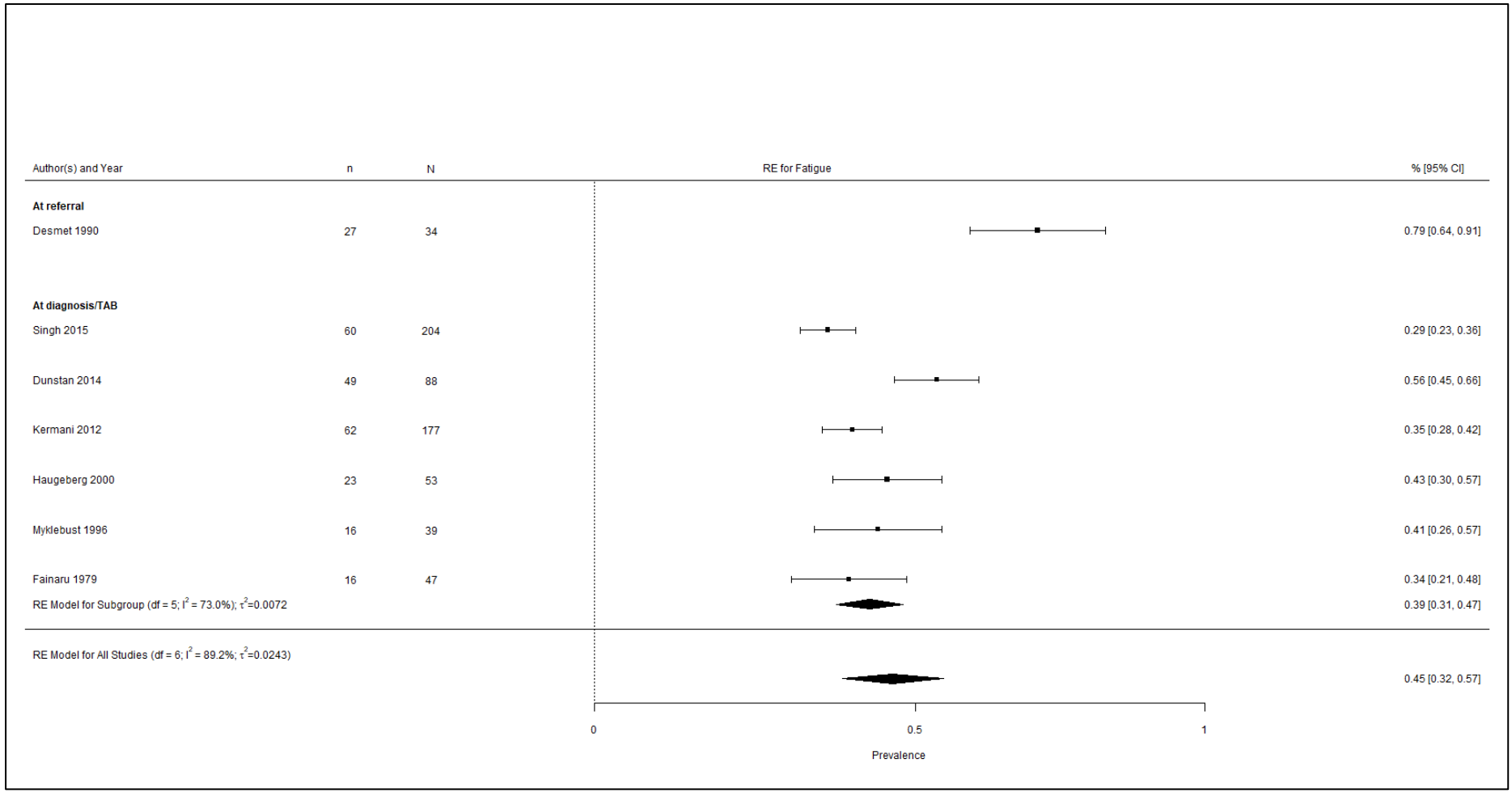

Figure 4: Meta-analysis forest plot for the prevalence of fatigue, stratified by point of recording, showing prevalence data, and 95% CI.

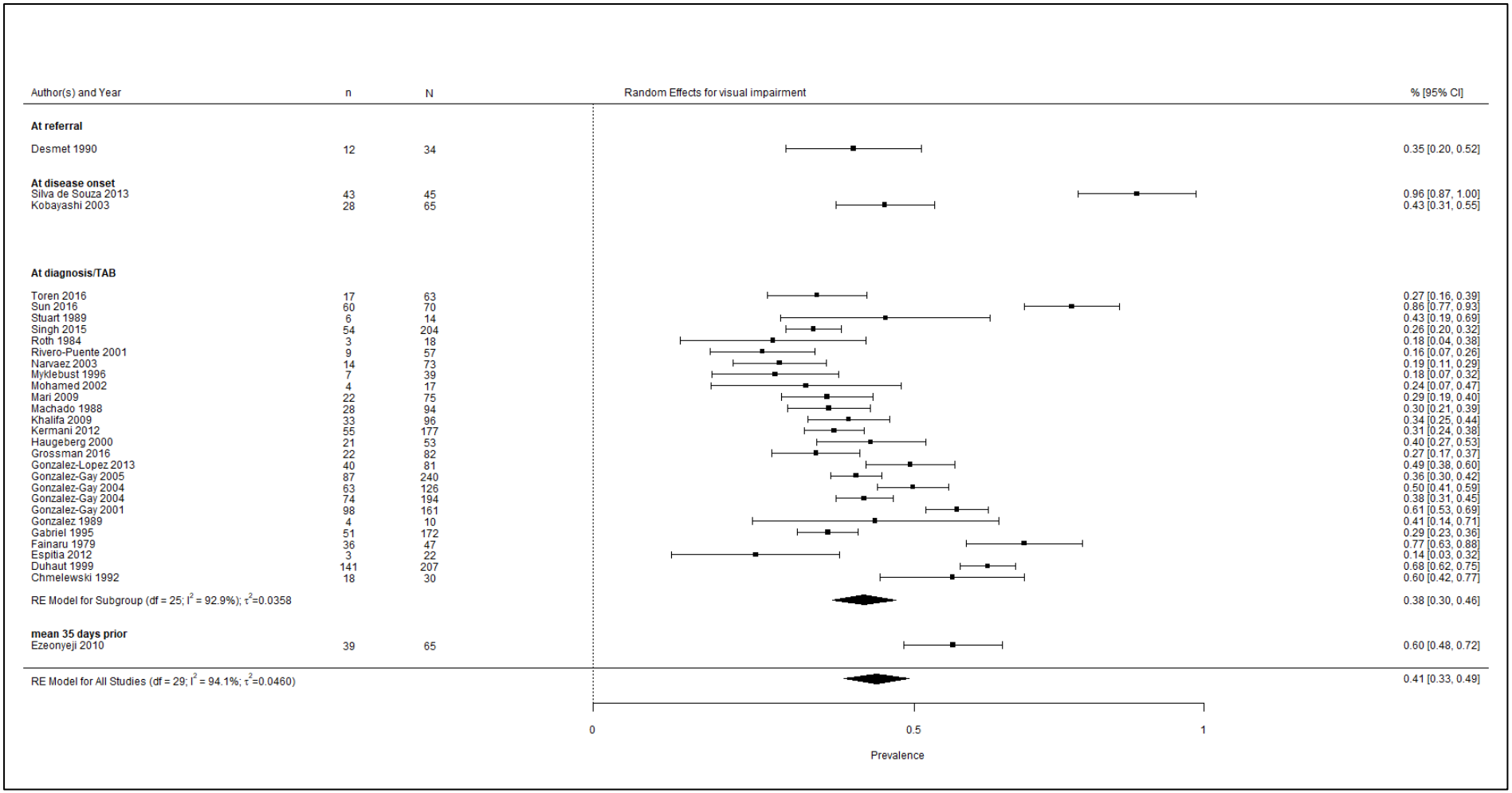

Figure 5: Meta-analysis forest plot for the prevalence of visual impairment, stratified by point of recording, showing prevalence data, and

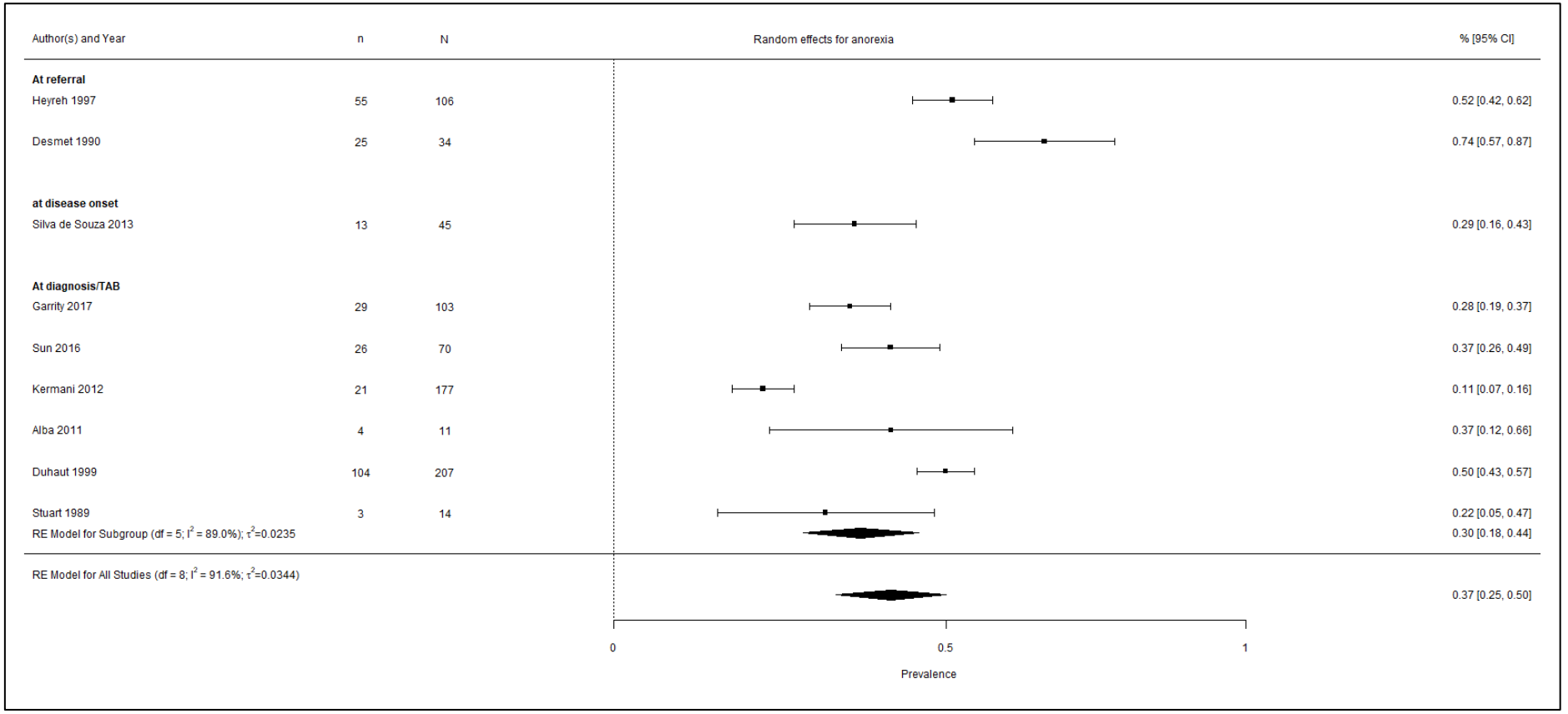

Figure 6: Meta-analysis forest plot for anorexia stratified by point of recording, showing raw prevalence data, and 95% CI.

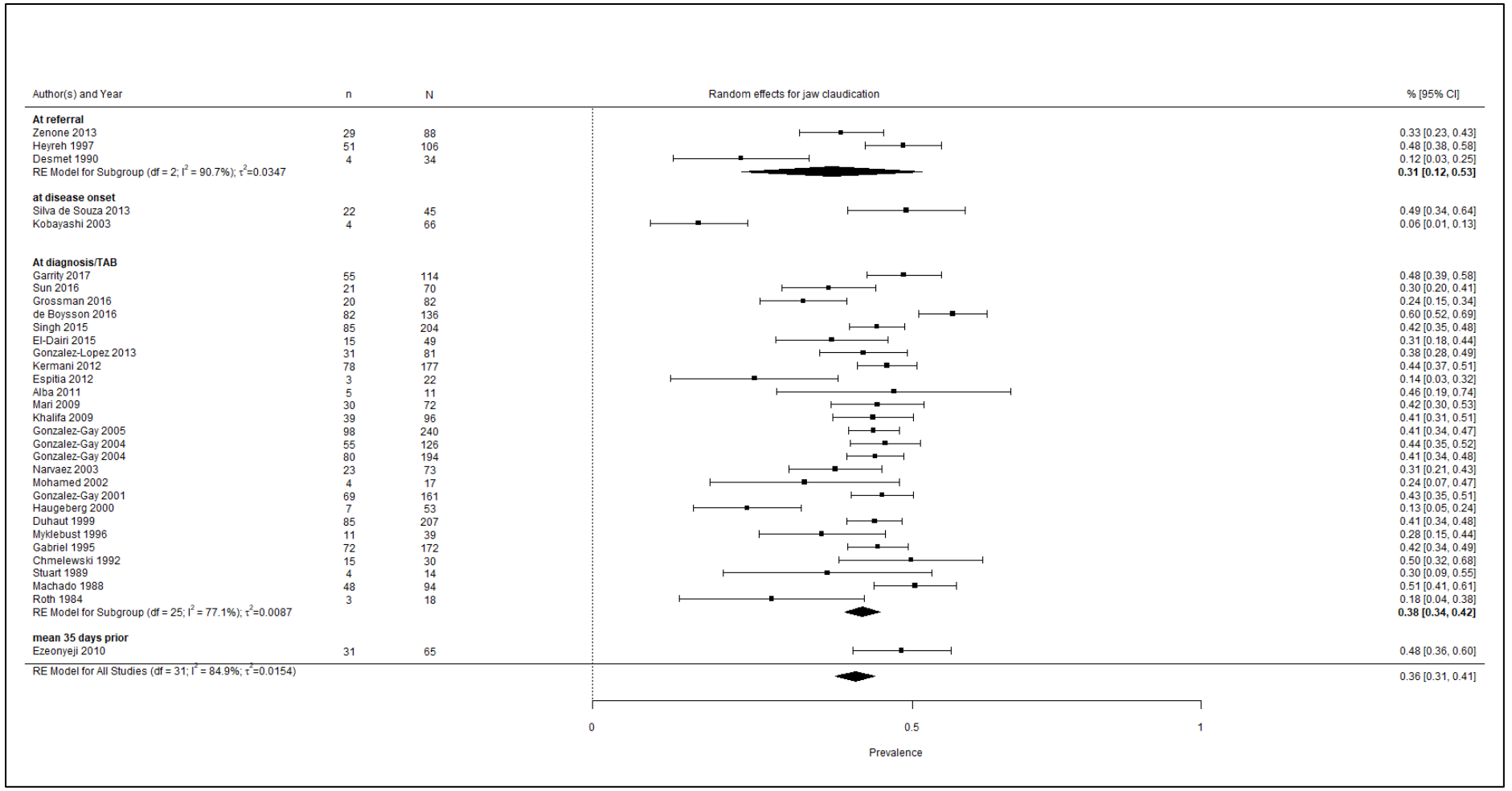

Figure 7: Meta-analysis forest plot for jaw claudication stratified by point of recording, showing raw prevalence data, and 95% CI.

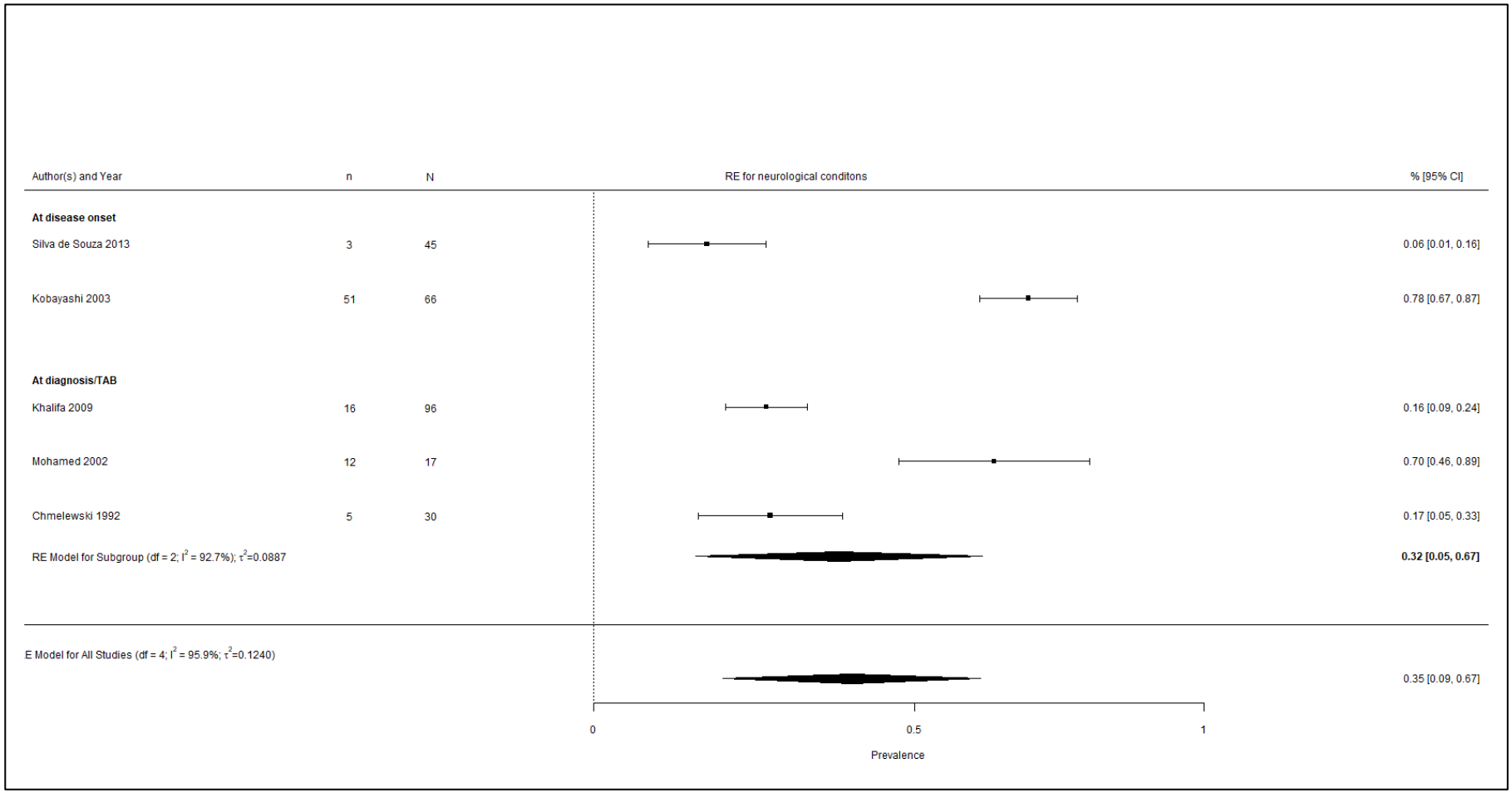

Figure 8: Meta-analysis forest plot for neurological conditions stratified by point of recording, showing raw prevalence data, and 95%

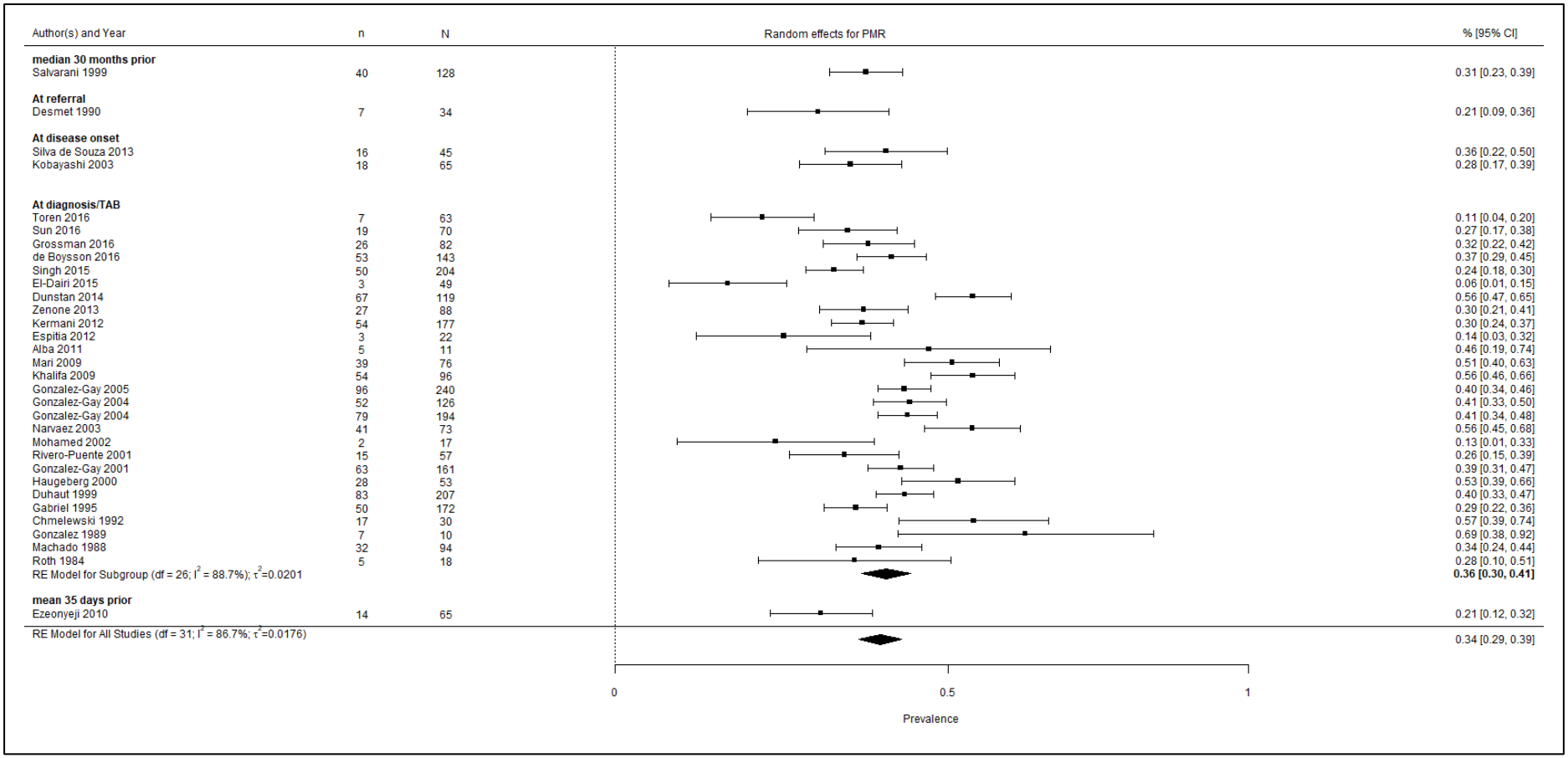

Figure 9: Meta-analysis forest plot for PMR stratified by point of recording, showing raw prevalence data, and 95% CI.

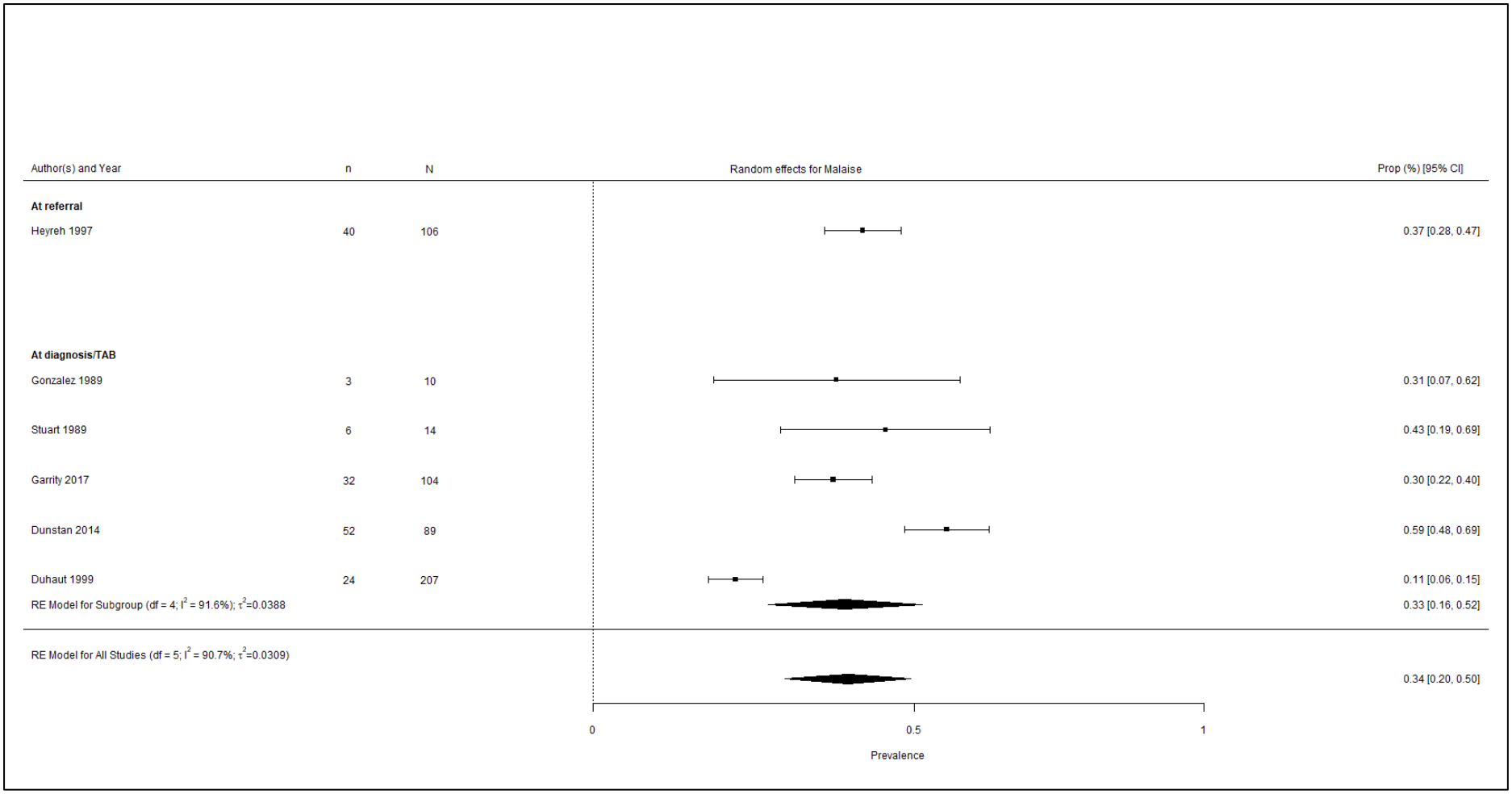

Figure 10: Meta-analysis forest plot for malaise stratified by point of recording, showing raw prevalence data, and 95% CI.

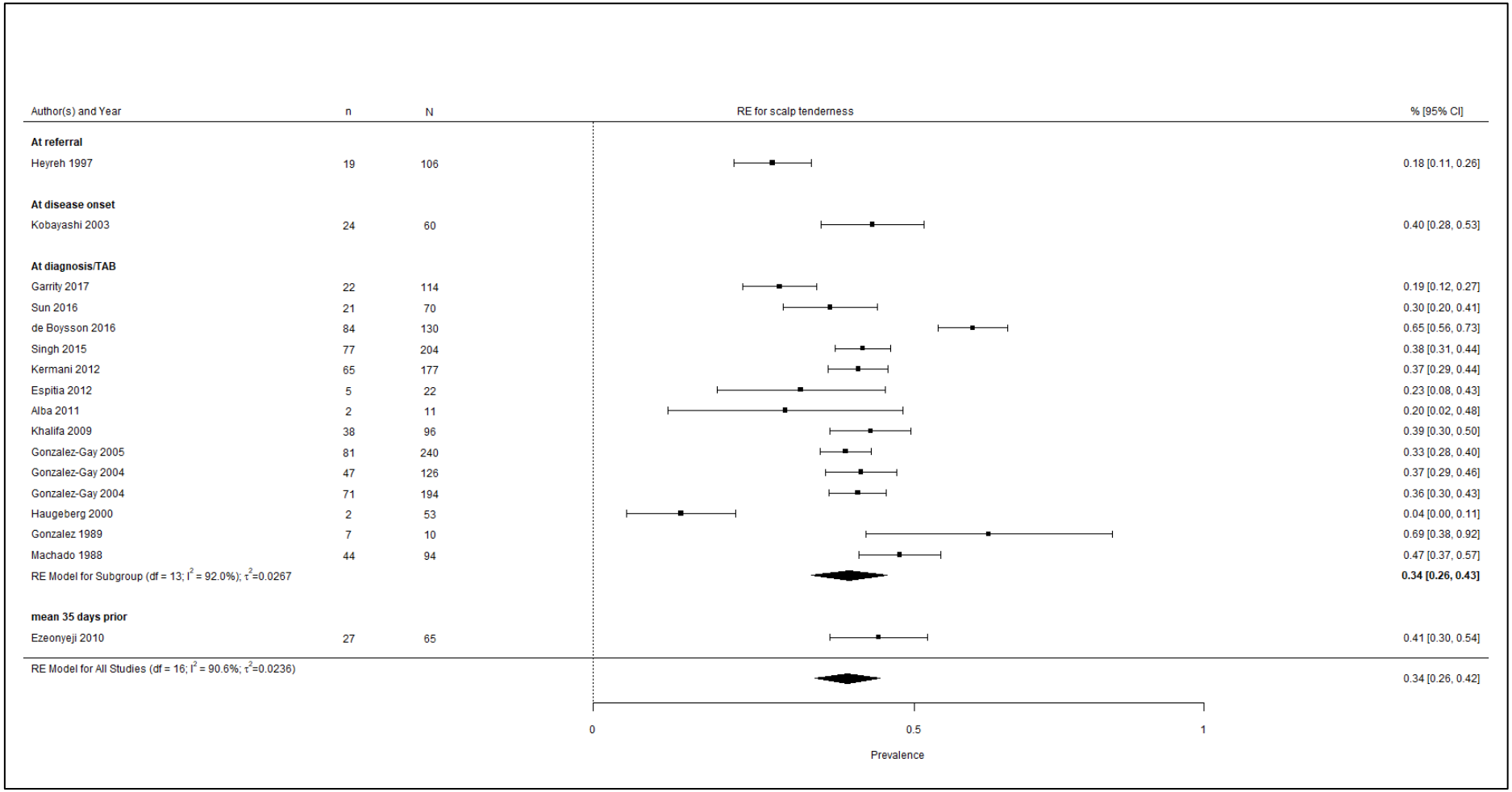

Figure 11: Meta-analysis forest plot for scalp tenderness stratified by point of recording, showing raw prevalence data, and 95% CI.

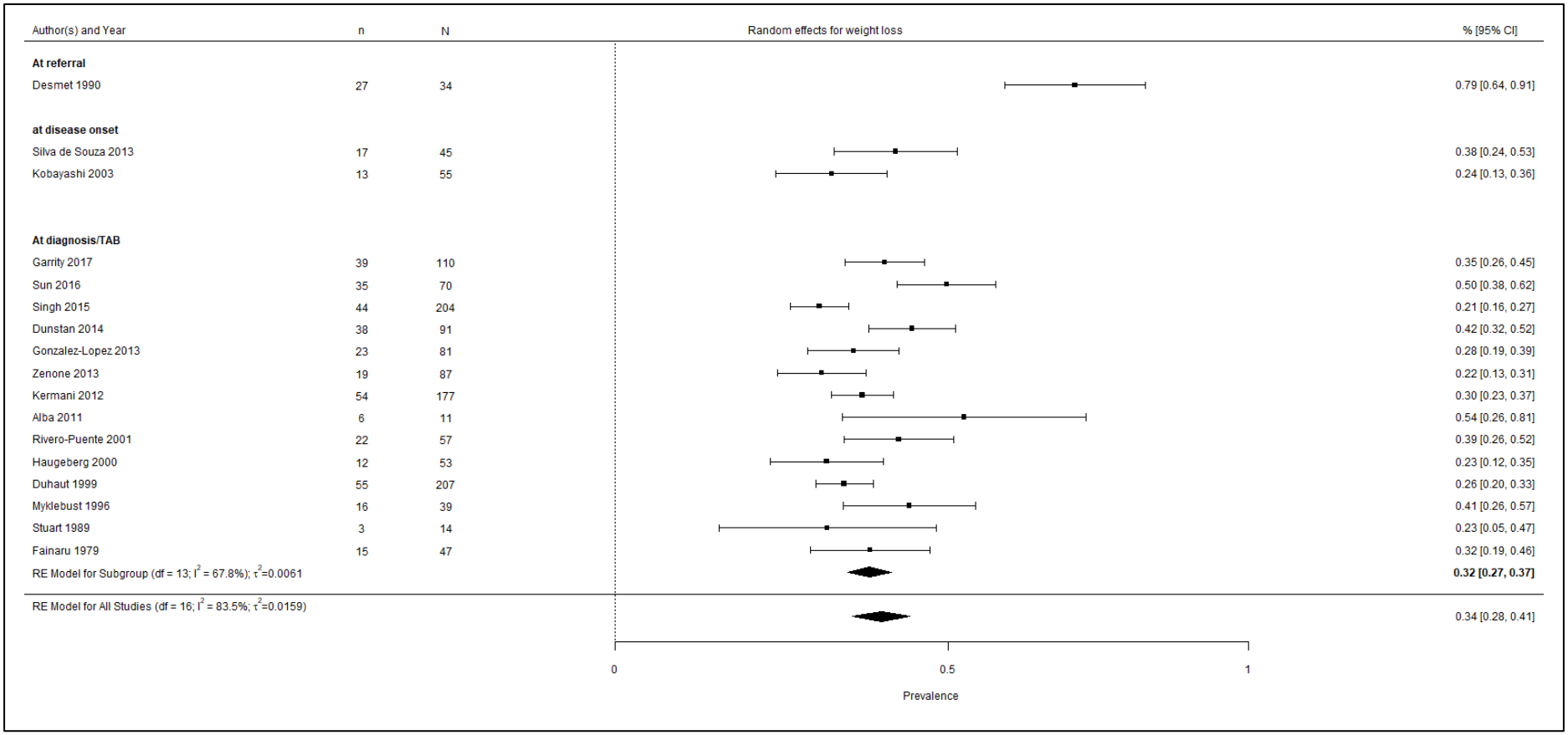

Figure 12: Meta-analysis forest plot for weight loss stratified by point of recording, showing raw prevalence data, and 95% CI.

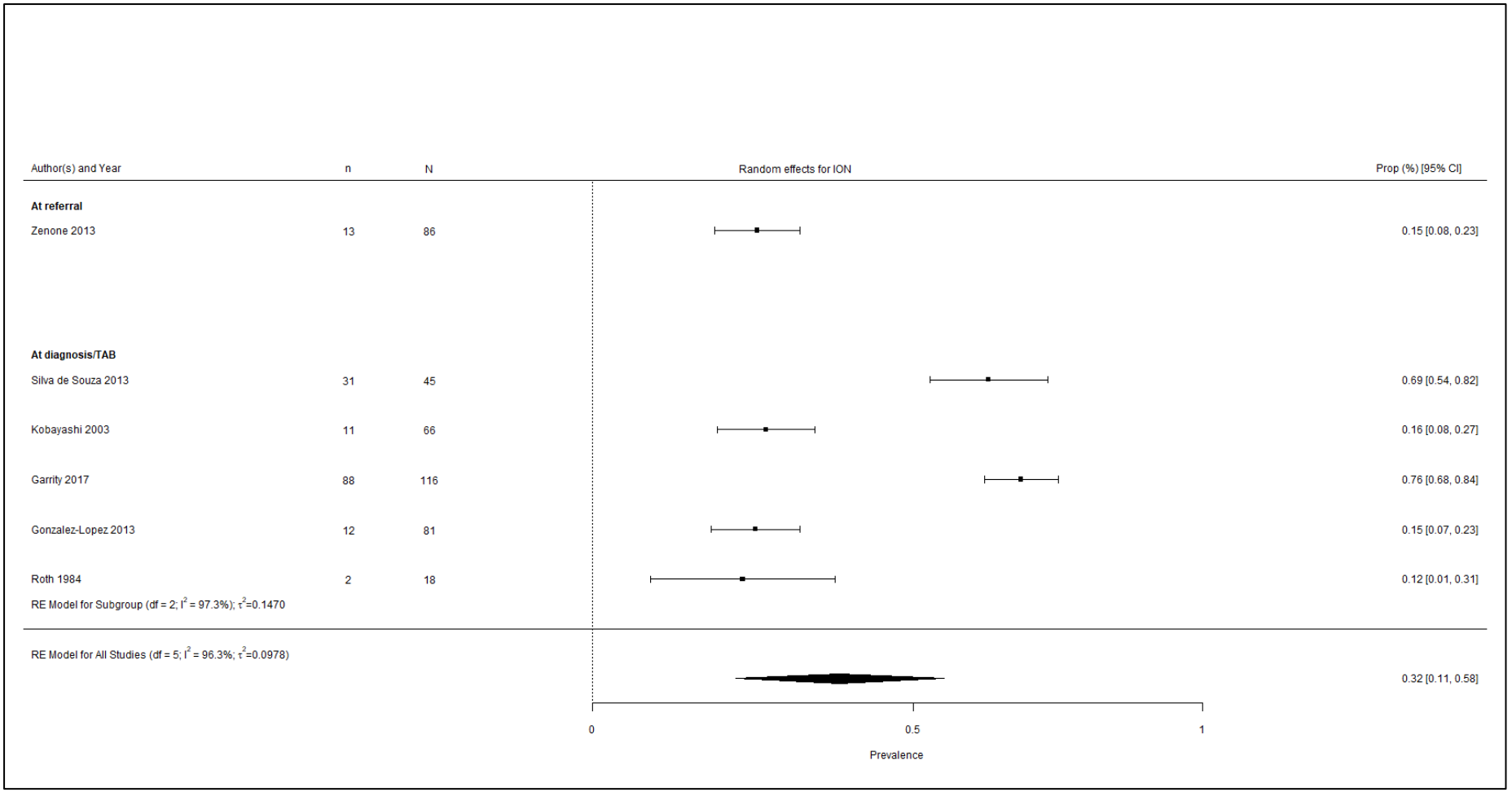

Figure 13: Meta-analysis forest plot for Ischaemic optic neuropathy (ION) stratified by point of recording, showing raw prevalence data,

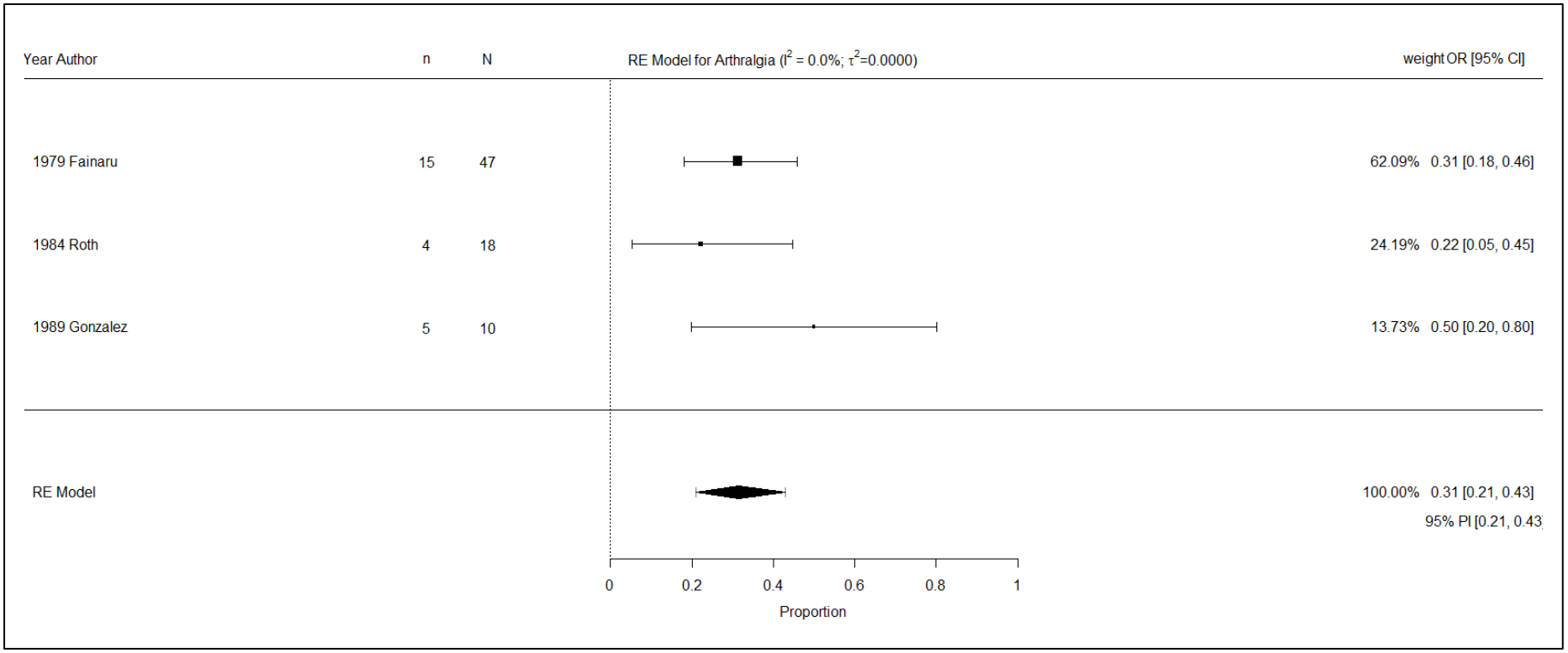

Figure 14: Meta-analysis forest plot for arthralgia stratified by point of recording, showing raw prevalence data, and 95% CI.

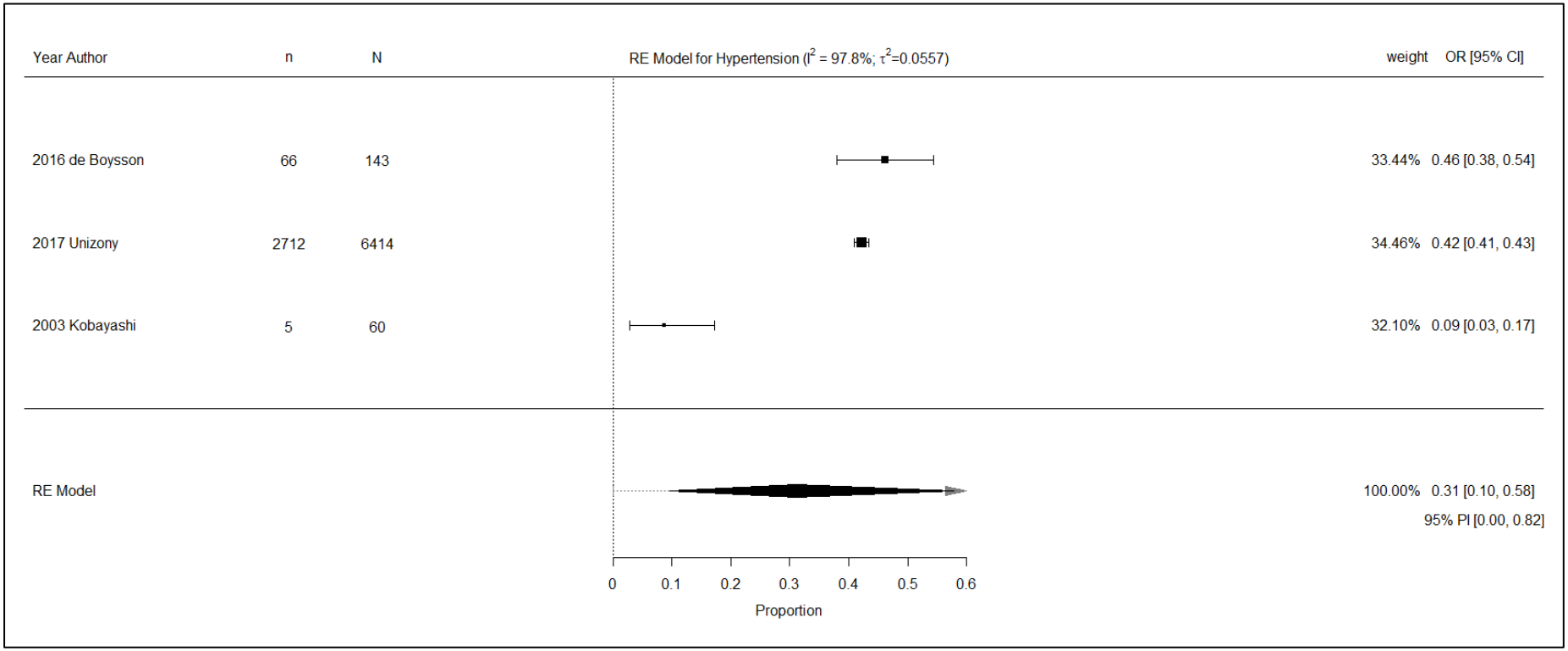

Figure 15: Meta-analysis forest plot for hypertension stratified by point of recording, showing raw prevalence data, and 95% CI.

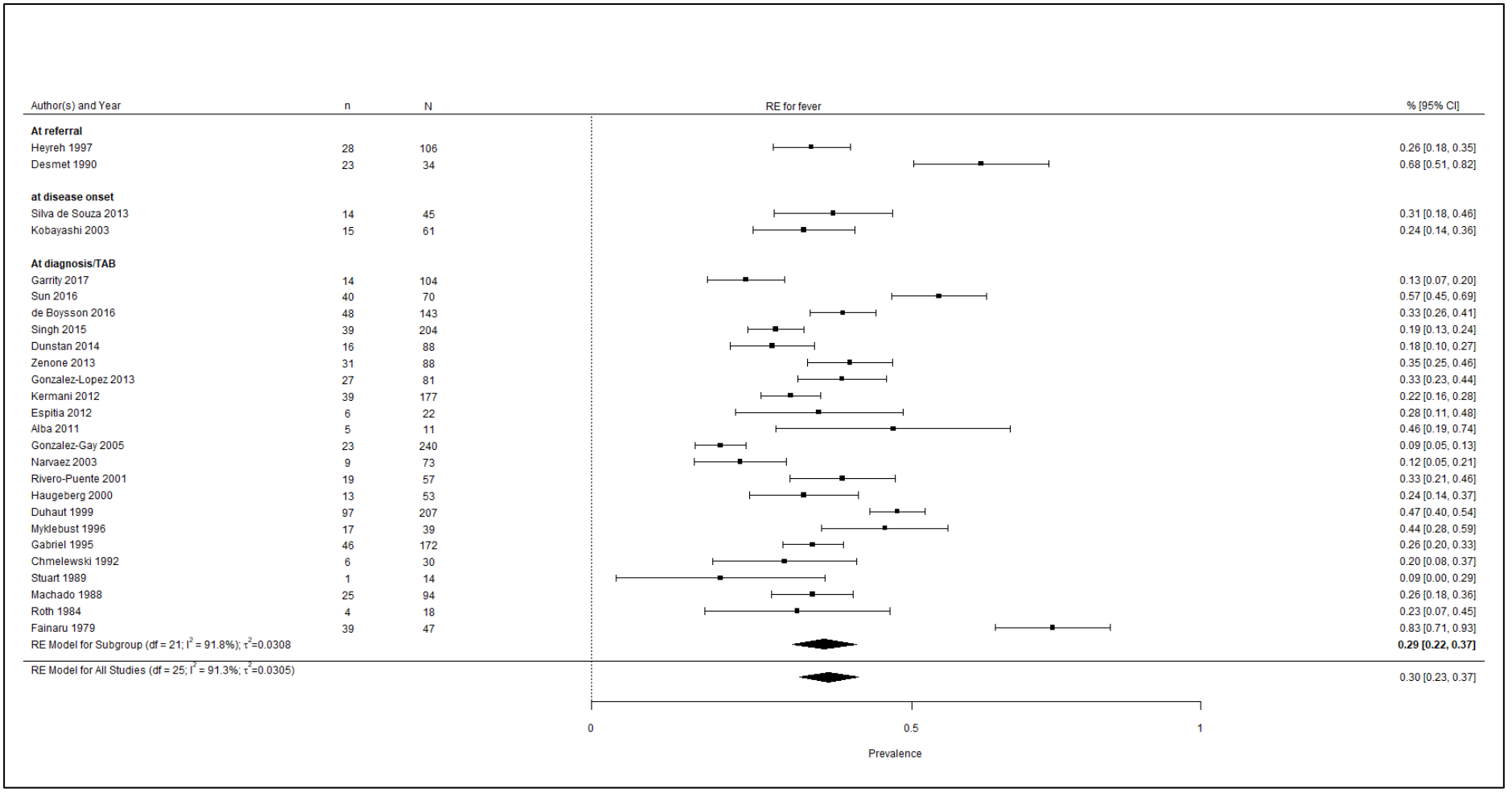

Figure 16: Meta-analysis forest plot for fever stratified by point of recording, showing raw prevalence data, and 95% CI.

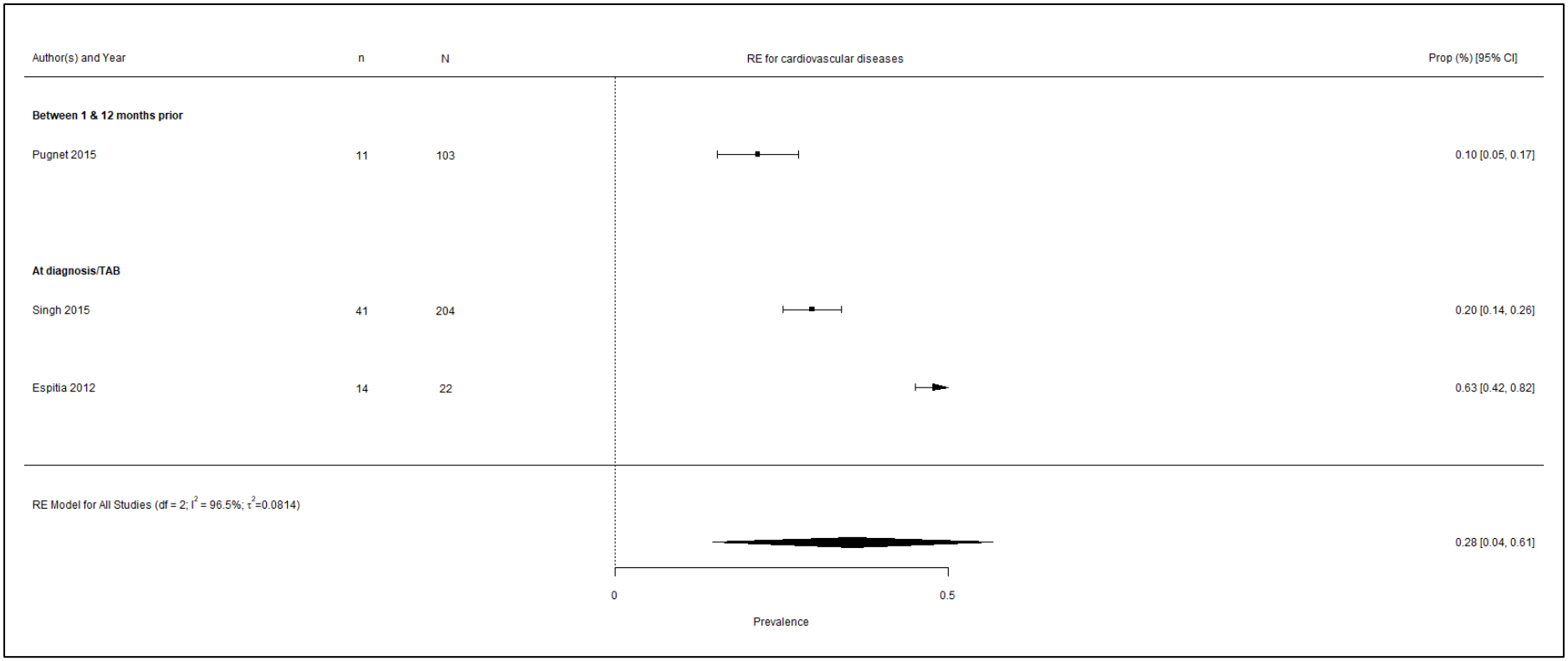

Figure 17: Meta-analysis forest plot for cardiovascular diseases stratified by point of recording, showing raw prevalence data, and 95% CI.

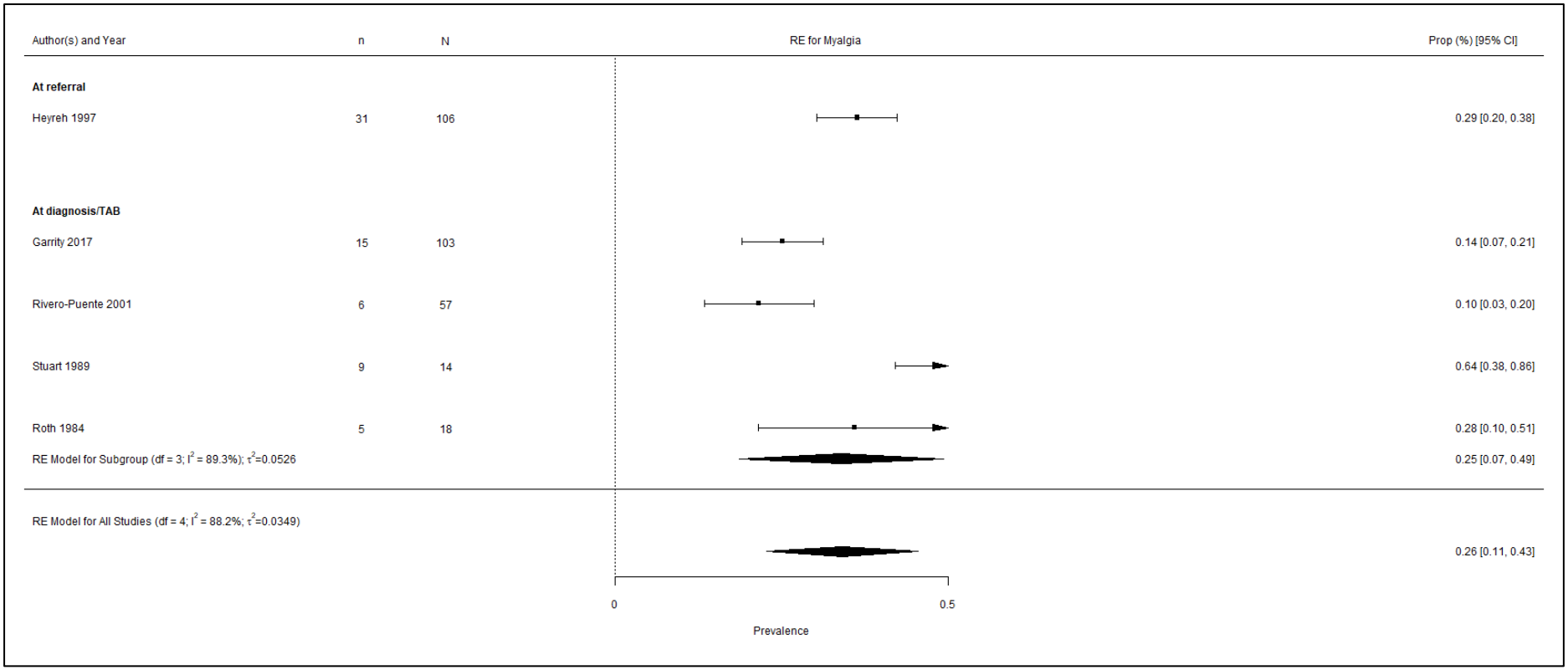

Figure 18: Meta-analysis forest plot for myalgia stratified by point of recording, showing raw prevalence data, and 95% CI.

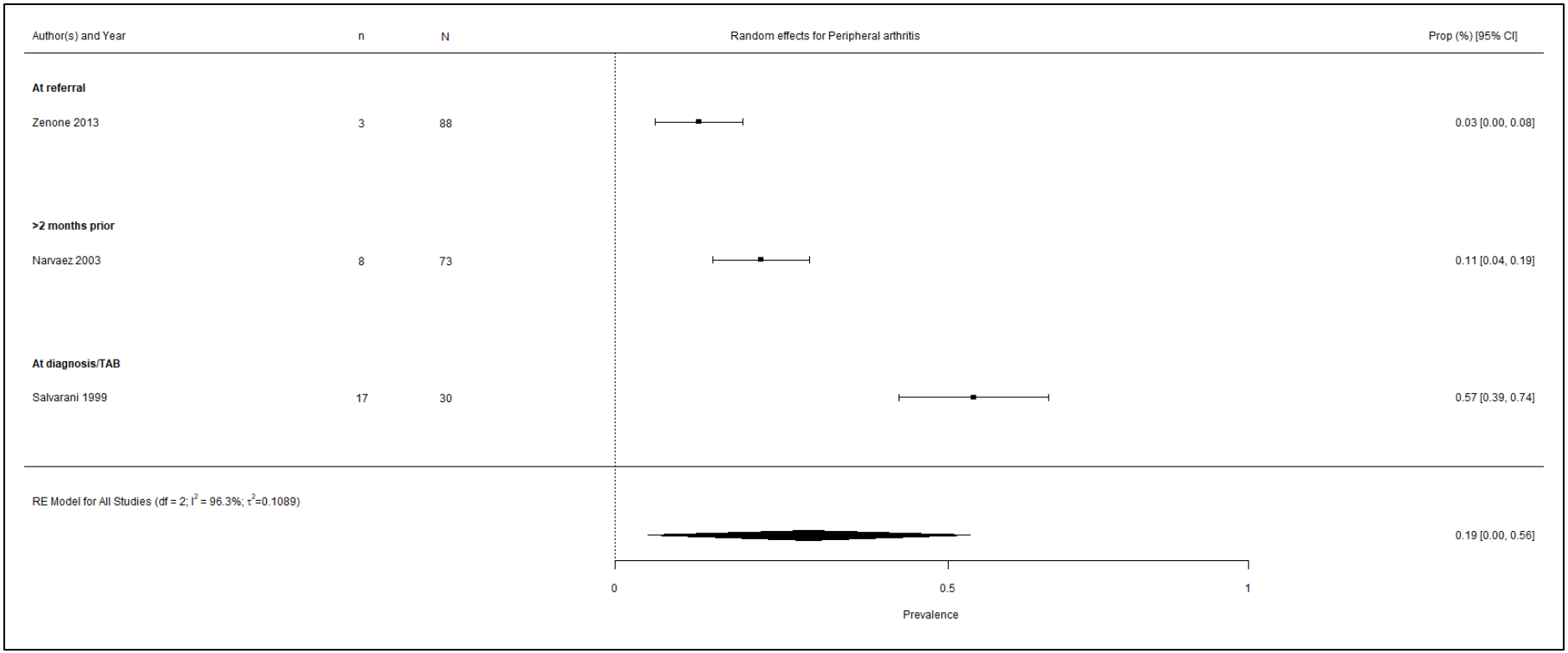

Figure 19: Meta-analysis forest plot for peripheral arthritis, showing raw prevalence data, weight of each study, study proportion, 95% CI,

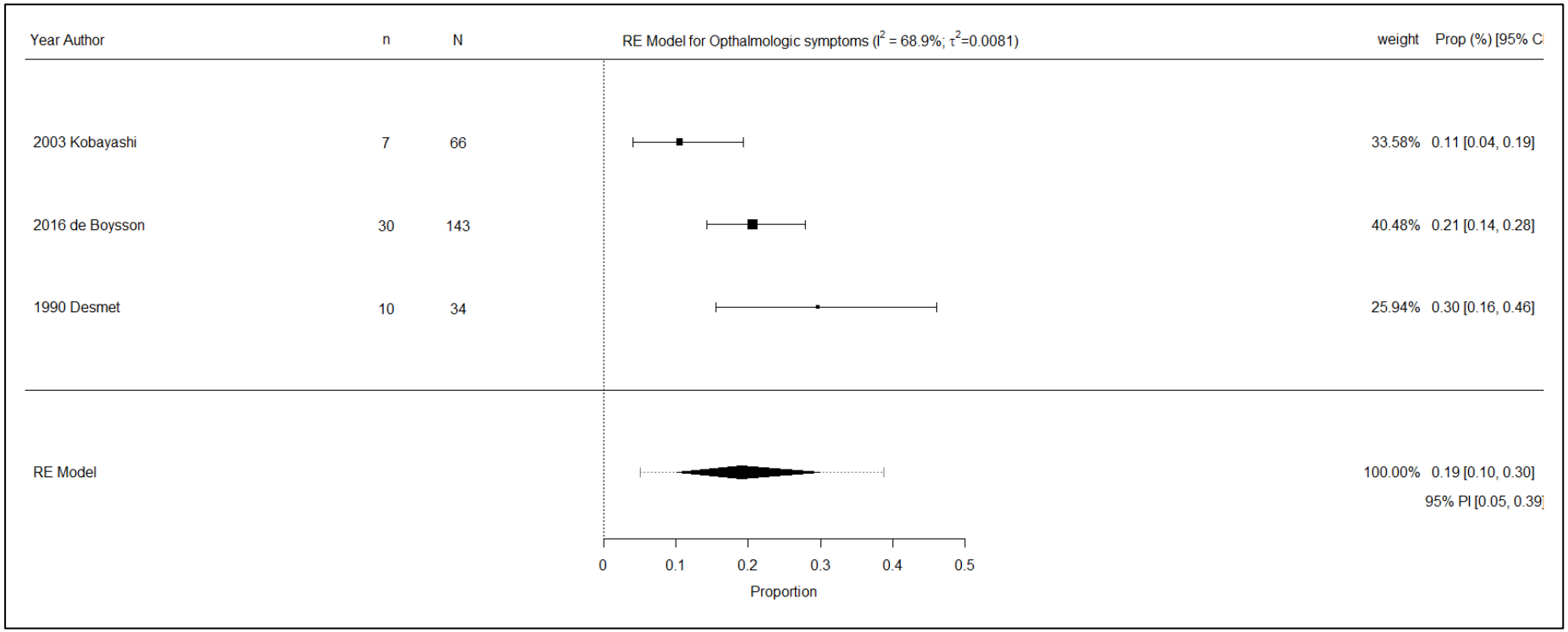

Figure 20: Meta-analysis forest plot for ophthalmologic symptoms, showing raw prevalence data, weight of each study, study

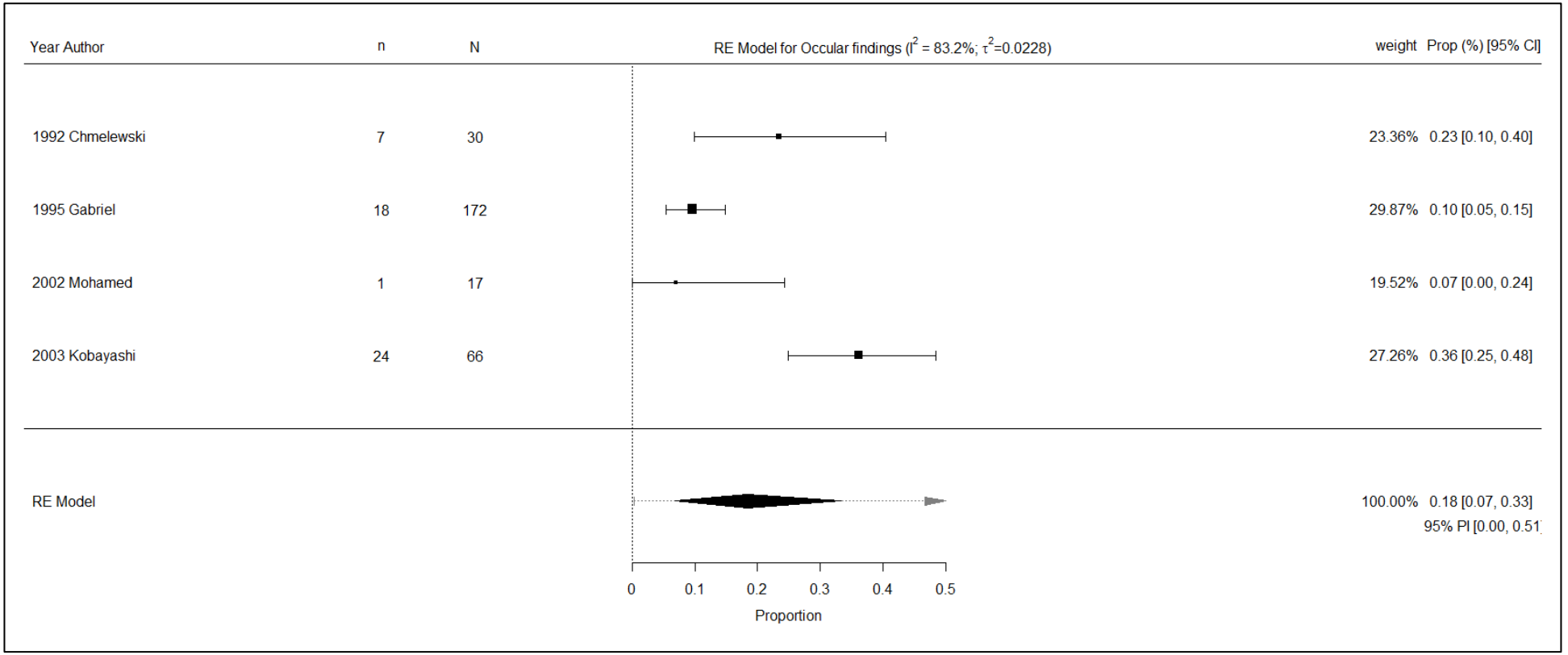

Figure 21: Meta-analysis forest plot for ocular findings, showing raw prevalence data, weight of each study, study proportion, 95% CI, and 95%

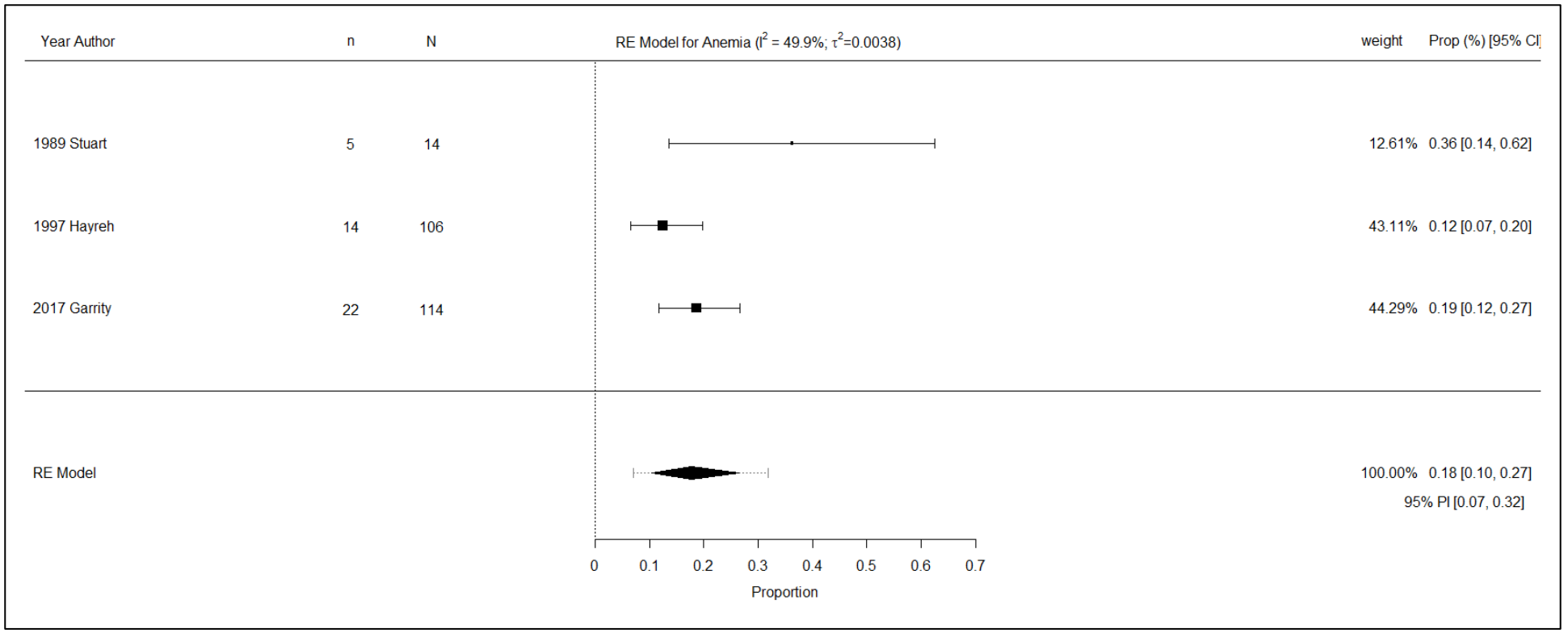

Figure 22: Meta-analysis forest plot for anaemia, showing raw prevalence data, weight of each study, study proportion, 95% CI, and 95% PI.

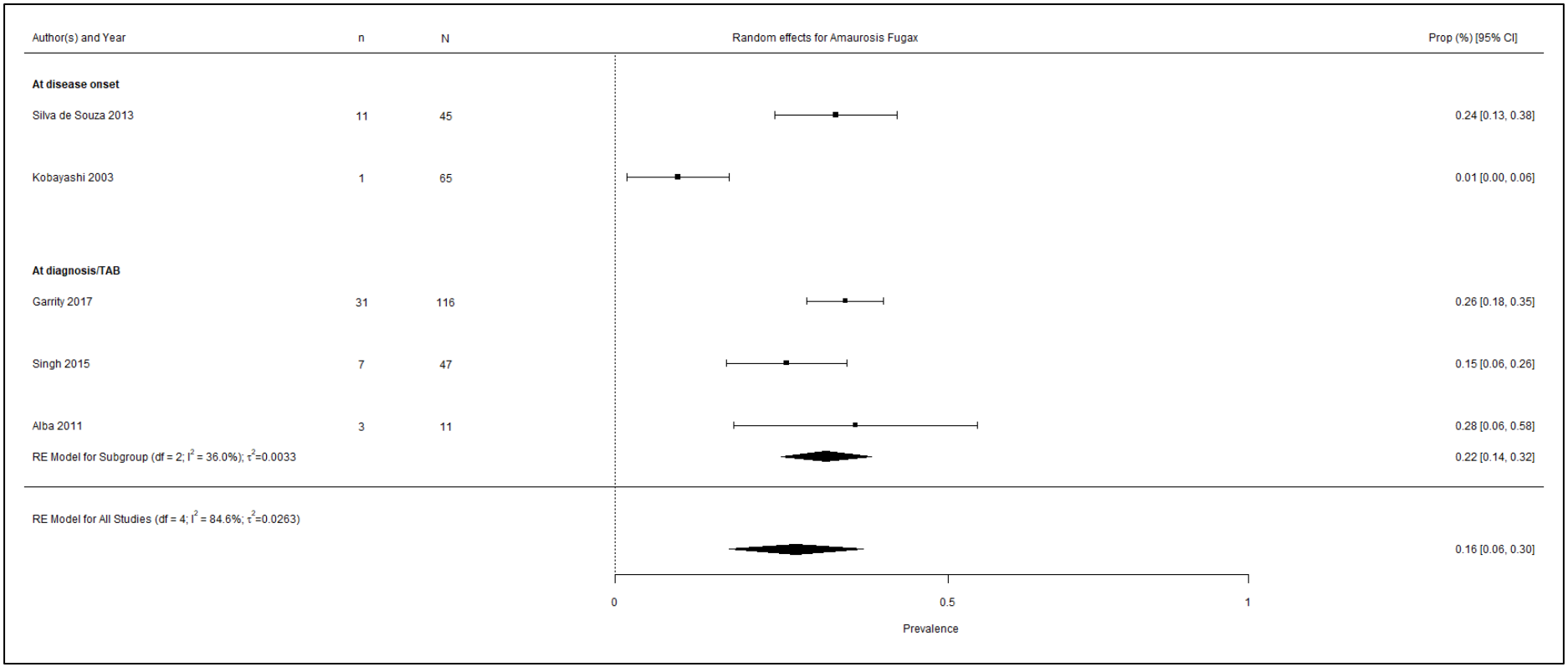

Figure 23: Meta-analysis forest plot for amaurosis fugax, showing raw prevalence data, study proportion, 95% CI, and 95% PI.

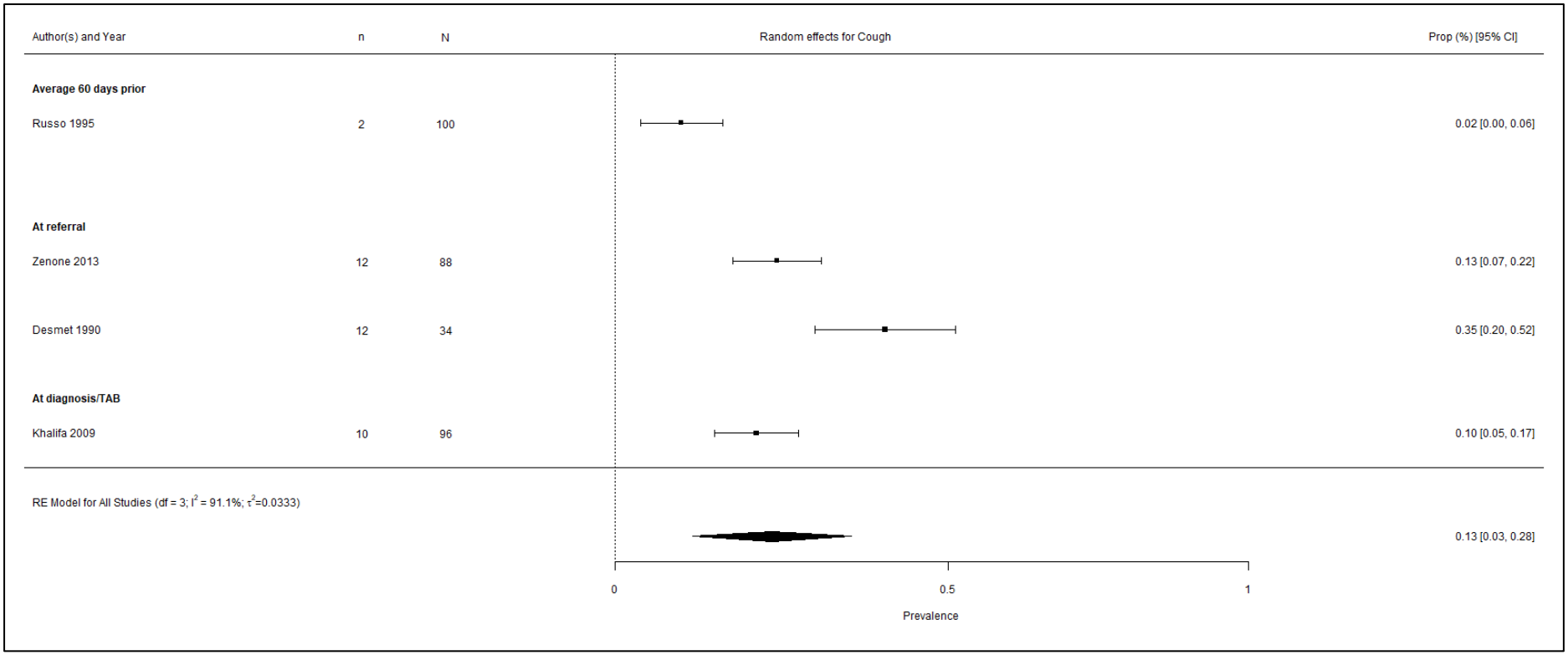

Figure 24: Meta-analysis forest plot for cough, showing raw prevalence data, study proportion, 95% CI, and 95% PI.

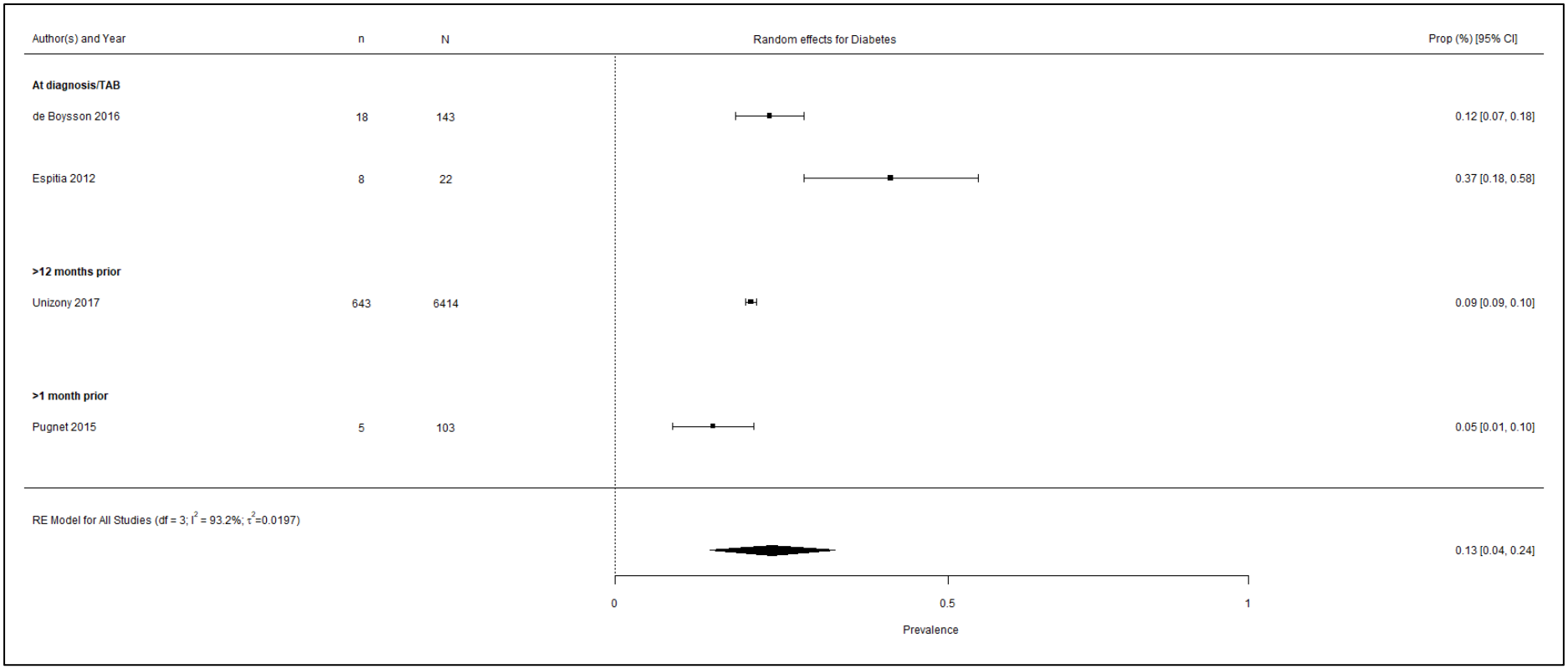

Figure 25: Meta-analysis forest plot for diabetes, showing raw prevalence data, study proportion, 95% CI, and 95% PI.

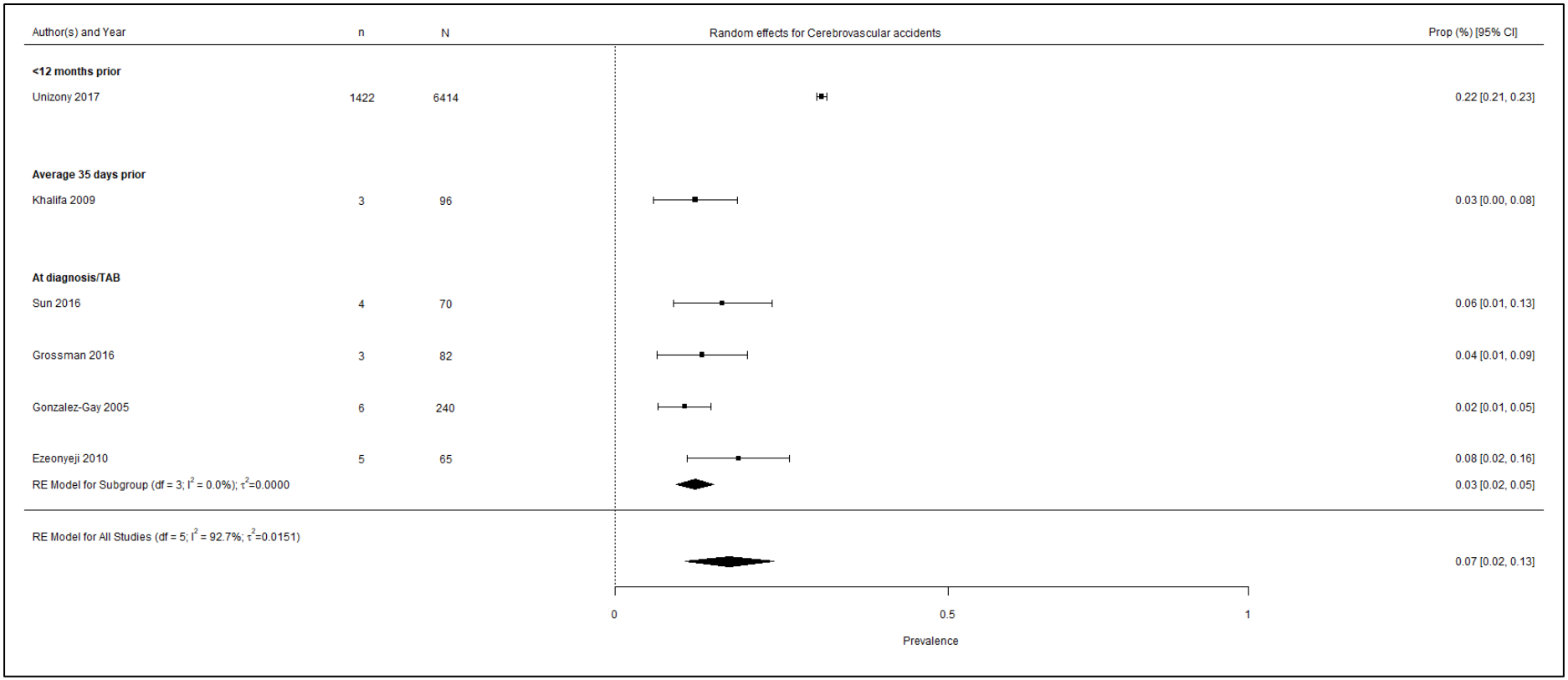

Figure 26: Meta-analysis forest plot for cerebrovascular accidents, showing raw prevalence data, study proportion, 95% CI, and 95% PI.

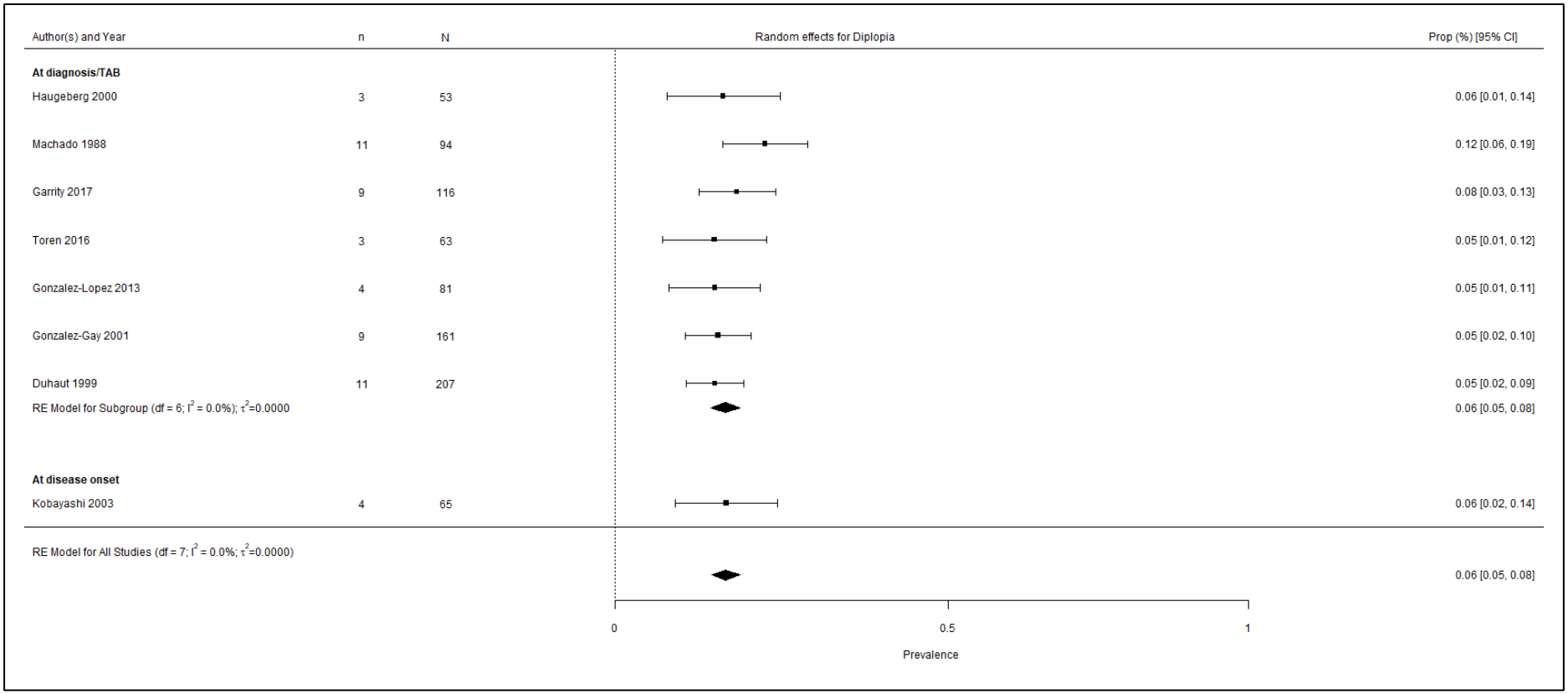

Figure 27: Meta-analysis forest plot for diplopia, showing raw prevalence data, study proportion, 95% CI, and 95% PI.

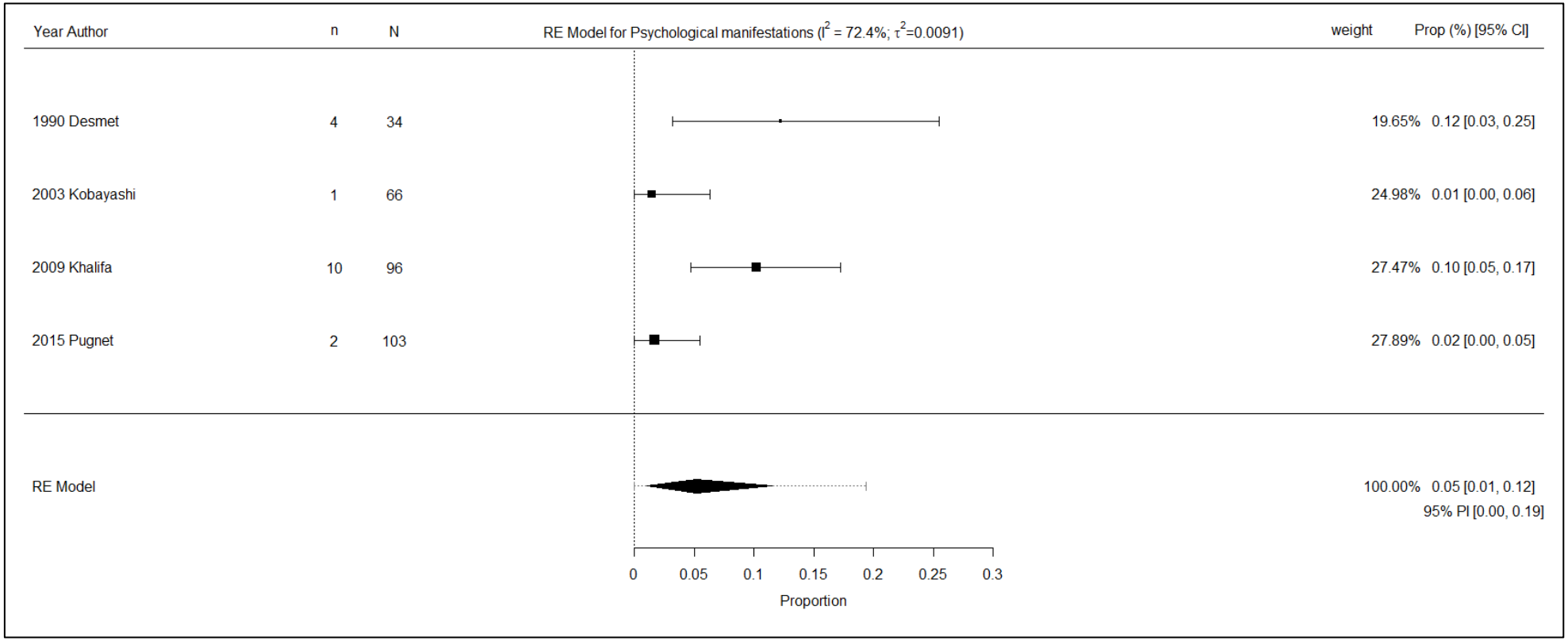

Figure 28: Meta-analysis forest plot for psychological manifestations, showing raw prevalence data, study proportion, 95% CI, and 95% PI.

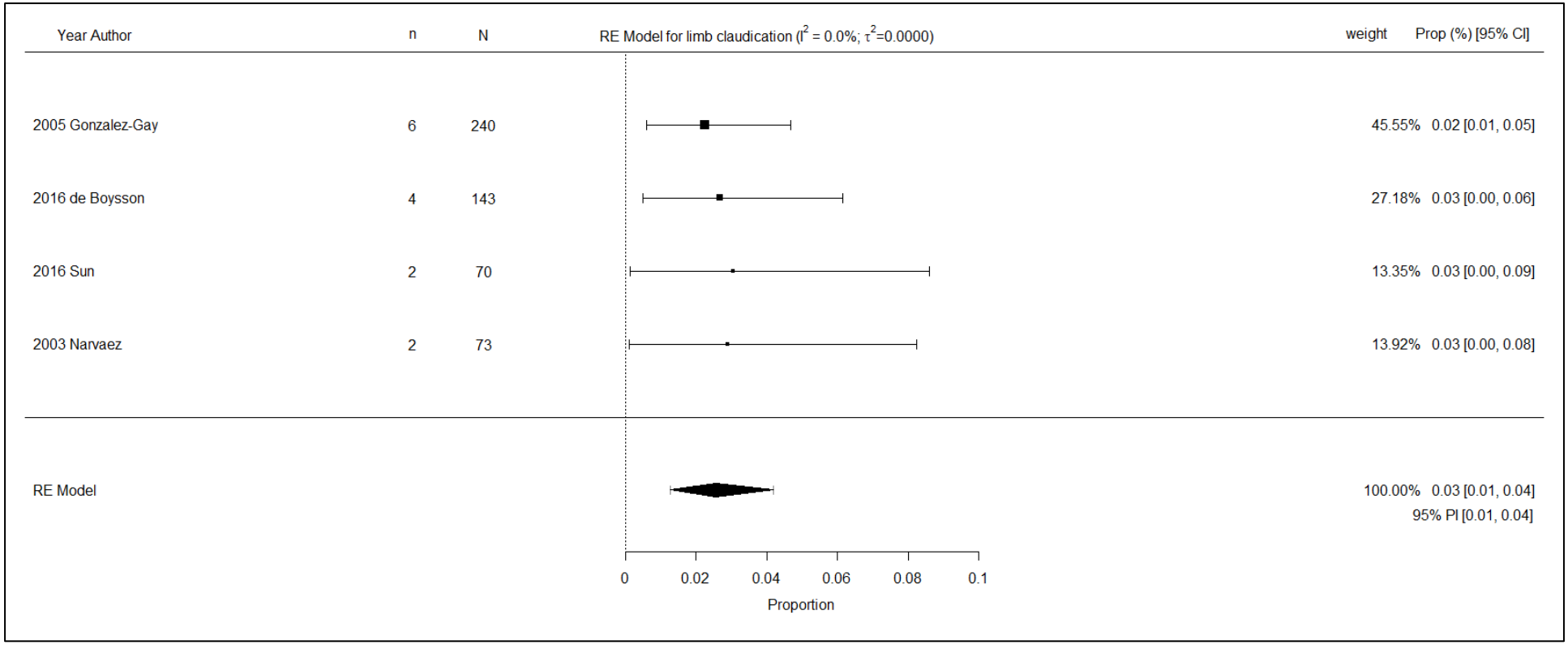

Figure 29: Meta-analysis forest plot for limb claudication, showing raw prevalence data, study proportion, 95% CI, and 95% PI.

Appendix 3.5 – Subgroup prevalence meta-analysis

Table 1: Subgroup meta-analysis showing frequency and prevalence for each subgroup, confidence intervals, and measures of heterogeneity.

Clinical feature	**Duration subgroup**	**N**	**Prevalence (%)**	**95% CI**	**I^2 (%)**	**τ^2**
Headache	At diagnosis/TAB	29	78	(72%, 83%)	89.3	0.02
constitutional/systemic symptoms	At diagnosis/TAB	27	62	(48%, 75)%	96.3	0.05
Abnormal TA	At diagnosis/TAB	27	58	(46%, 70%)	95.6	0.06
Fatigue	At diagnosis/TAB	6	39	(31%, 47%)	73.0	0.01
Any visual impairment	At diagnosis/TAB	27	38	(30%, 46%)	92.9	0.04
Jaw Claudication	At diagnosis/TAB	26	38	(34%, 42%)	77.1	0.01
PMR	At diagnosis/TAB	27	36	(30%, 41%)	88.7	0.02

Scalp tenderness	At diagnosis/TAB	14	34	(26%, 43%)	92.0	0.03
Neurological conditions	At diagnosis/TAB	3	32	(5%, 67%)	92.7	0.09
Weight loss	At diagnosis/TAB	14	32	(27%, 37%)	67.8	0.01
Anorexia	At diagnosis/TAB	6	30	(18%, 44%)	89.0	0.02
Fever	At diagnosis/TAB	22	29	(22%, 37%)	91.8	0.03
Cardiovascular diseases	At diagnosis/TAB	4	18	(1%, 47%)	97.1	0.10

Appendix 3.6 – Meta-regression

Table 1: Results of the meta-regression showing beta coefficients, 95% confidence intervals, levels of significance, and model fit (R^2).

Clinical feature	I^2 (%)	Covariates	Univariable				Multivariable			
Headache	89.3		Coef.	95% CI	P-value	R^2 (%)	Coef.	95% CI	P-value	R^2 (%)
		Continent (ref = Americas)				5.10				27.12
		Europe	0.126	(-0.005, 0.256)	<0.1		0.041	(-0.114, 0.196)		
		Other	0.066	(-0.107, 0.240)			0.06	(-0.111, 0.230)		
		Study quality (ref = Good)				5.38				
		Fair	0.127	(-0.001, 0.256)			0.081	(-0.047, 0.208)		
		Poor	0.036	(-0.209, 0.282)			-0.031	(-0.266, 0.204)		
		Study design				0				

		(ref = case-control)								
		Cohort	0.136	(-0.190, 0.461)						
		Proportion female	-0.003	(-0.007, 0.001)						
		Year of publication **(ref = 1970-2000)**				**37.57**				
		2001-2010	**0.158**	**(0.029, 0.287)**	**<0.05**		0.119	(-0.060, 0.297)		
		2011-present	**-0.056**	**(-0.181, 0.069)**			-0.052	(-0.187, 0.083)		
		Type of diagnosis (ref = TAB)				0				
		ACR	-0.025	(-0.239, 0.188)						
		ACR/TAB	0.076	(-0.080, 0.232)						
		Other	0.103	(-0.252, 0.458)						
		Mean age	-0.016	(-0.046, 0.015)		0				
Constitutional/	96.4	**Continent** **(ref = Americas)**				52.2				**96.50%**

Systemic symptoms										
		Europe	0.481	(0.214, 0.748)	<0.001		**0.601**	**(0.254, 0.948)**	**<0.001**	
		Other	0.465	(0.128, 1.802)	<0.01		**0.691**	**(0.404, 0.977)**	**<0.001**	
		Study quality (ref = Good)								
		Fair	-0.11	(-0.404, 0.184)		0.00				
		Proportion female	0.012	(0.004, 0.019)	<0.01	49.60	**-0.001**	**(-0.005, 0.004)**		
		Year of publication (ref = 1970-2000)				30.50				
		2001-2010	-0.059	(-0.369, 0.212)			**-0.317**	**(-0.455, -0.179)**	**<0.001**	
		2011-present	-0.449	(-0.846, -0.052)	<0.05		**-0.46**	**(-0.688, -0.232)**	**<0.001**	
		Type of diagnosis (ref = TAB)				0.00				
		ACR/TAB	0.141	(-0.170, 0.453)						

		Other	-0.006	(-0.545, 0.533)						
		Mean age	-0.027	(-0.149, 0.095)		0.00				
Abnormal temporal artery	95.8	**Continent (ref = Americas)**				24.32				**41.71%**
		Europe	0.326	(0.074, 0.577)	<0.05		**0.114**	**(-0.241, 0.469)**		
		Other	0.158	(-0.118, 0.434)			**0.122**	**(-0.140, 0.383)**		
		Study quality (ref = Good)				0.00				
		Fair	0.051	(-0.209, 0.311)						
		Poor	0.25	(-0.280, 0.780)						
		Proportion female	-0.005	(-0.019, 0.008)		0.00				
		Year of publication (ref = 1970-2000)				46.19				
		2001-2010	0.292	(0.076, 0.507)	<0.01		**0.219**	**(-0.135, 0.574)**		
		2011-present	-0.09	(-0.328, 0.247)			**-0.125**	**(-0.387, 0.138)**		

		Type of diagnosis (ref = TAB)				0.00				
		ACR	-0.028	(-0.435, 0.380)						
		ACR/TAB	0.078	(-0.218, 0.374)						
		Mean age	0.006	(-0.028, 0.041)		0.00				
Any visual impairment	92.9	Continent (ref = Americas)				9.76				21.22
		Europe	0.042	(-0.129, 0.212)			0.036	(-0.158, 0.230)		
		Other	0.225	(0.007, 0.443)	<0.05		0.171	(-0.147, 0.489)		
		Study quality (ref = Good)				**30.51**				
		Fair	**-0.06**	**(-0.214, 0.094)**			-0.042	(-0.230, 0146)		
		Poor	**0.352**	**(0.088, 0.616)**	**<0.01**		0.309	(-0.010, 0.627)	<0.1	
		Study design (ref = case-control)				0				

		Cohort	-0.118	(-0.518, 0.283)						
			-0.039	(-0.240, 0.162)						
		Proportion female	0	(-0.006, 0.006)		0				
		Year (ref = 1970-2000)				0				
		2001-2010	-0.083	(-0.271, 0.104)						
		2011-present	-0.05	(-0.251, 0.151)						
		Type of diagnosis (ref = TAB)				0				
		ACR	-0.172	(-0.471, 0.128)						
		ACR/TAB	0.042	(-0.149, 0.234)						
		Other	0.014	(-0.403, 0.430)						
		Mean age	-0.031	(-0.069, 0.006)	<0.1	8.06	0.001	(-0.047, 0.050)		
Jaw claudication	77.1	Continent (ref = Americas)				5.23				

		Europe	-0.05	(-0.144, 0.044)						
		Other	-0.11	(-0.244, 0.024)						
		Study quality (ref = Good)				7.70				
		Fair	-0.075	(-0.164, 0.015)						
		Poor	-0.057	(-0.215, 0.101)						
		Study design (ref = case-control)				0.00				
		Cohort	-0.004	(-0.227, 0.219)						
		Proportion female	0.001	(-0.001, 0.004)		0.59				
		Year (ref = 1970-2000)				0.00				
		2001-2010	0.043	(-0.073, 0.158)						
		2011-present	0.034	(-0.078, 0.146)						
		Type of diagnosis (ref = TAB)				37.50				

		ACR	0.064	(-0.044, 0.172)						
		ACR/TAB	-0.024	(-0.113, 0.065)						
		Other	-0.295	(-0.497, -0.092)	<0.01					
		Mean age	0.012	(-0.005, 0.028)		14.24				
PMR	88.7	**Continent** **(ref = Americas)**				12.31				**53.97**
		Europe	0.089	(-0.035, 0.214)			**0.087**	**(-0.041, 0.215)**		
		Other	0.14	(-0.030, 0.310)			**0.228**	**(0.083, 0.373)**	**<0.01**	
		Study quality **(ref = Good)**				0.00				
		Fair	-0.027	(-0.177, 0.123)			**-0.02**	**(-0.169, 0.129)**		
		Poor	-0.048	(-0.302, 0.206)			**-0.169**	**(-0.298, -0.039)**	**<0.05**	
		Proportion female	0.004	(-0.001, 0.008)		1.56	**0.005**	**(0.001, 0.009)**	**<0.05**	
		Year of publication (ref = 1970-2000)				19.37				

		2001-2010	-0.007	(-0.150, 0.137)						
		2011-present	-0.149	(-0.288, -0.010)	<0.05					
		Type of diagnosis (ref = TAB)				0.00				
		ACR	-0.018	(-0.198, 0.162)						
		ACR/TAB	0.031	(-0.113, 0.175)						
		Other	0.184	(-0.146, 0.513)						
		Mean age	-0.01	(-0.043, 0.023)		0.00				
Scalp Tenderness	90.6	Continent (ref = Americas)				0.00				
		Europe	-0.013	(-0.229, 0.203)						
		Other	0.098	(-0.201, 0.397)						
		Study quality (ref = Good)				29.28				**70.58**
		Fair	-0.247	(-0.428, -0.065)	<0.01		**-0.178**	**(-0.310, -0.047)**	**<0.01**	

		Poor	-0.223	(-0.554, 0.107)			**-0.199**	**(-0.456, 0.058)**		
		Proportion female	-0.003	(-0.015, 0.009)		0.00				
		Year (ref = 1970-2000)				0.00				
		2001-2010	0.043	(-0.248, 0.335)						
		2011-present	0.013	(-0.257, 0.283)						
		Type of diagnosis (ref = TAB)				51.02				
		ACR	0.102	(-0.081, 0.286)			**0.088**	**(-0.063, 0.240)**		
		ACR/TAB	0.009	(-0.156, 0.174)			**0.017**	**(-0.134, 0.169)**		
		Other	-0.42	(-0.700, -0.140)	<0.01		**-0.37**	**(-0.607, -0.134)**	**<0.01**	
		Mean age	-0.006	(-0.084, 0.073)		0.00				
Weight loss		Continent (ref = Americas)				33.88				95.98
		Europe	-0.015	(-0.122, 0.093)			-0.043	(-0.142, 0.056)		
		Other	0.099	(-0.026, 0.223)			-0.132	(-0.410, 0.145)		

		Study quality (ref = Good)				0.00				
		Fair	0.013	(-0.129, 0.156)						
		Poor	0.01	(-0.247, 0.268)						
		Study design (ref = case-control)				0.00				
		Cohort	0.042	(-0.161, 0.245)						
		Proportion female	-0.003	(-0.006, -0.001)	<0.05	44.20	-0.003	(-0.008, 0.002)		
		Year (ref = 1970-2000)				0.00				
		2001-2010	0.101	(-0.130, 0.332)						
		2011-present	0.042	(-0.079, 0.162)						
		Type of diagnosis (ref = TAB)				7.57				
		ACR	-0.092	(-0.226, 0.043)			-0.049	(-0.137, 0.038)		

		ACR/TAB	0.026	(-0.116, 0.169)			0.015	(-0.098, 0.129)		
		Other	-0.028	(-0.190, 0.135)			-0.118	(-0.286, 0.051)		
		Mean age	**-0.025**	**(-0.037, -0.014)**	**<0.001**	**99.98**	-0.025	(-0.071, 0.021)		
Fever	91.8	**Continent** **(ref = Americas)**				10.20				**67.41**
		Europe	0.066	(-0.101, 0.233)			**0.108**	**(-0.030, 0.246)**		
		Other	0.205	(-0.015, 0.426)	<0.01		**0.594**	**(0.281, 0.907)**	**<0.01**	
		Study quality (ref = Good)				1.76				
		Fair	0.078	(-0.090, 0.246)						
		Poor	0.23	(-0.058, 0.517)						
		Study design (ref = case-control)				0.00				
		Cohort	-0.047	(-0.426, 0.333)						
		Proportion female	-0.005	(-0.011, 0.001)	<0.1	9.88				

		Year (ref = 1970-2000)				5.78				
		2001-2010	-0.197	(-0.433, 0.039)						
		2011-present	-0.054	(-0.221, 0.113)						
		Type of diagnosis (ref = TAB)								
		ACR	0.09	(-0.121, 0.302)						
		ACR/TAB	0.086	(-0.123, 0.294)						
		Other	-0.01	(-0.416, 0.396)		0.00				
		Mean age	-0.036	(-0.068, -0.004)	<0.05	24.92	**0.018**	**(-0.019, 0.055)**		

R^2 = Overall model fit.

Results in bold indicate the final meta-regression model.

Appendix 3.7 – Forest plots for association meta-analysis

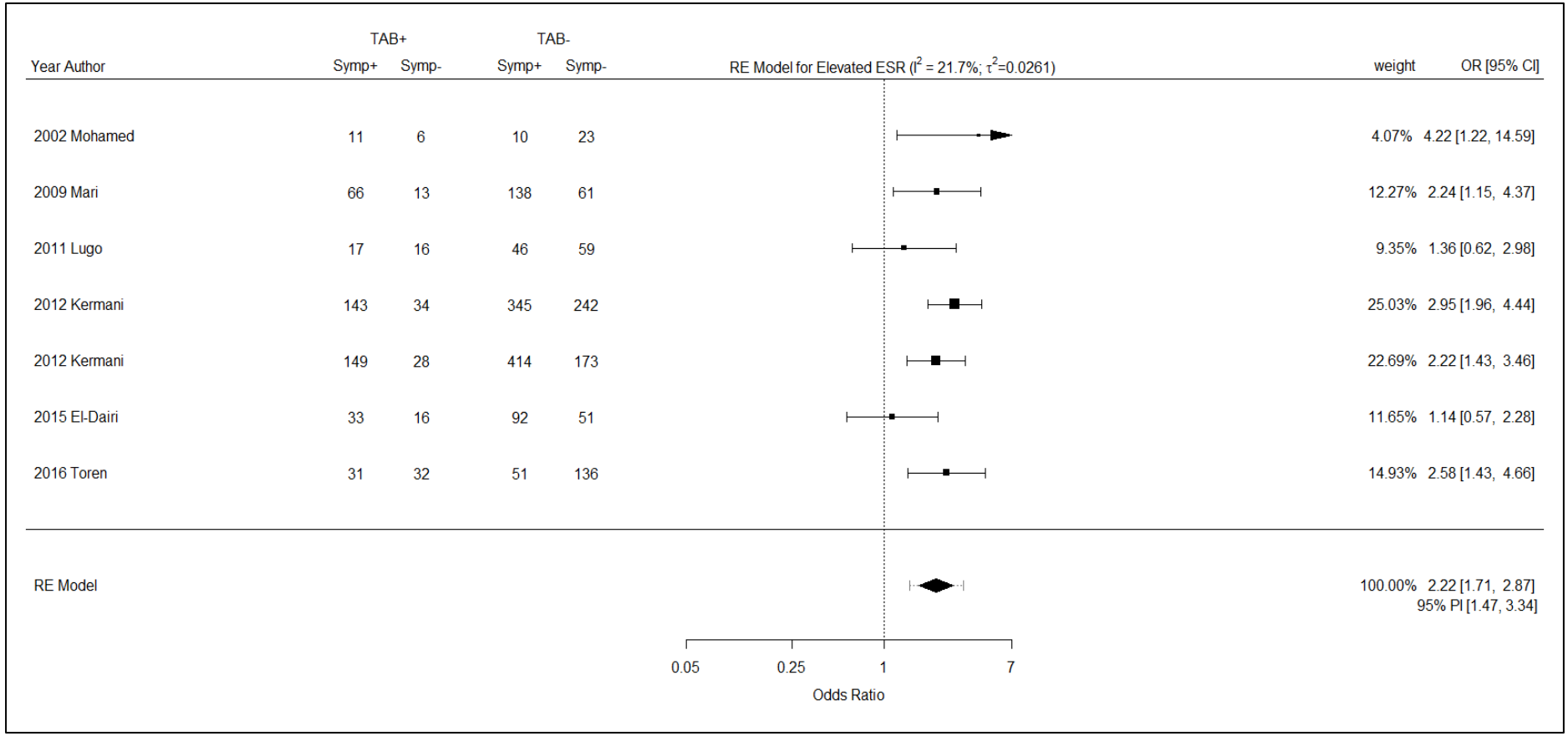

Figure 1: Forest plot of the association between elevated ESR and a subsequent diagnosis of GCA, showing odds ratios for each study, the pooled odds ratio, the weight of each study, and the 95% confidence interval.

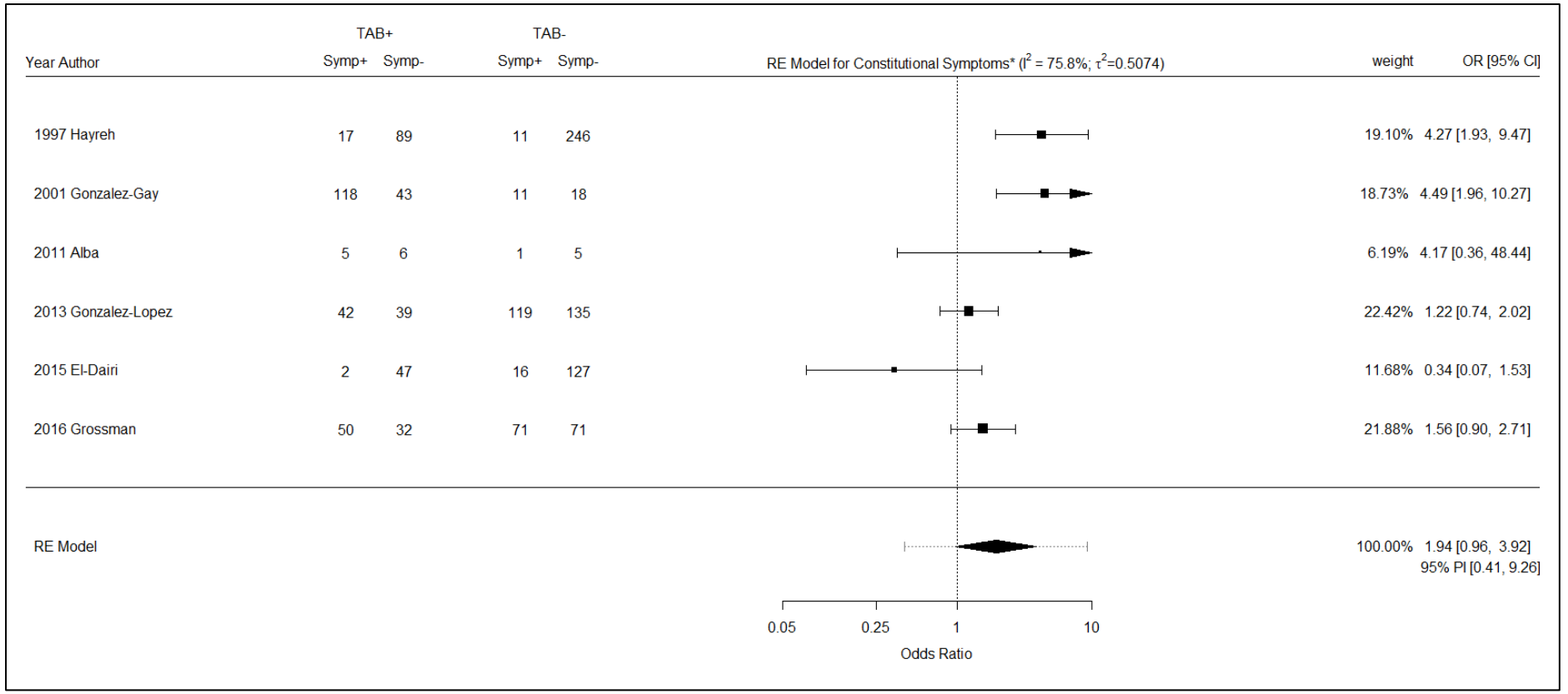

Figure 2: Forest plot of the association between constitutional/systemic symptoms and a subsequent diagnosis of GCA, showing odds ratios for each study, the pooled odds ratio, the weight of each study, and the 95% confidence interval.

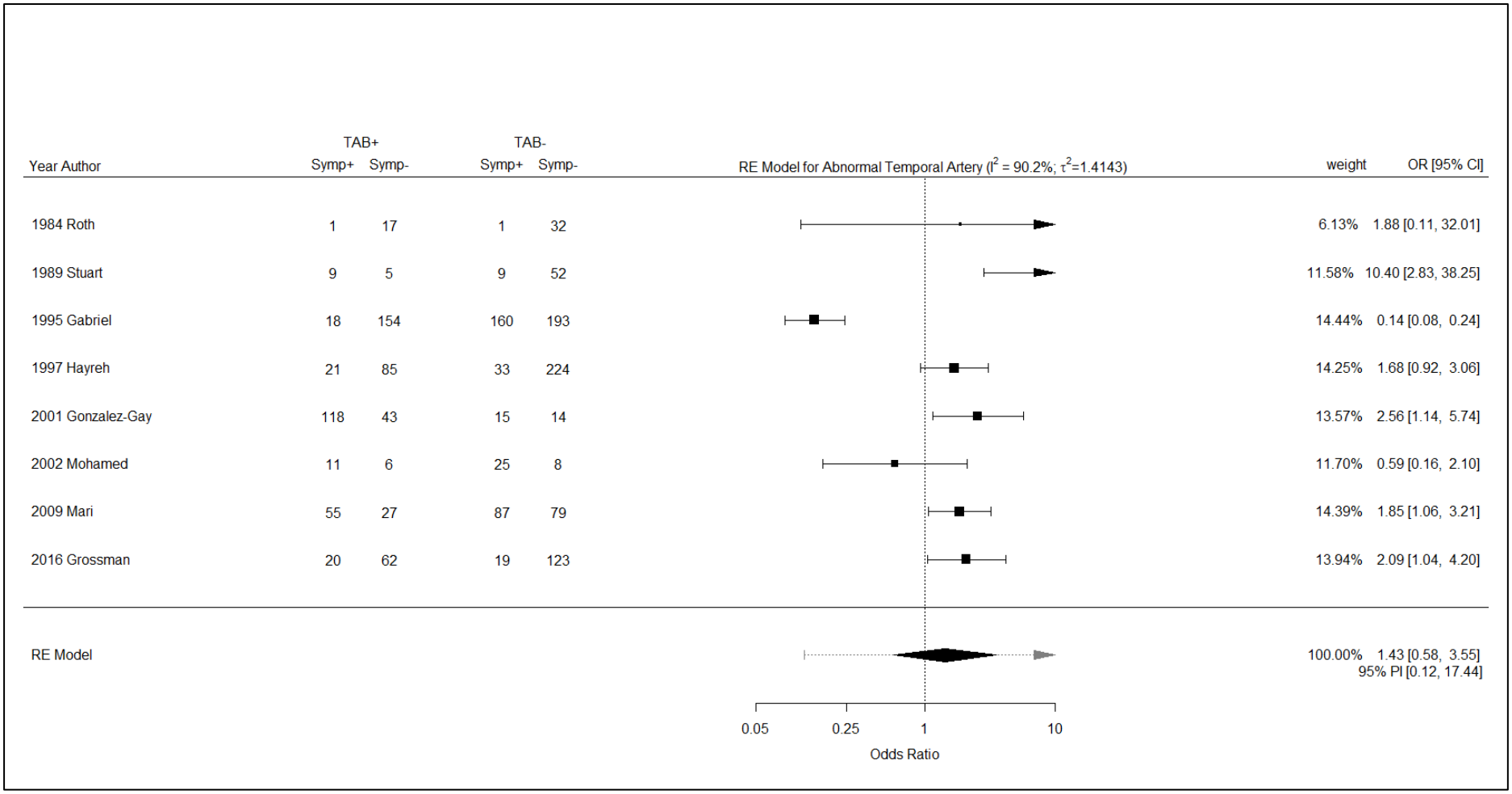

Figure 3: Forest plot of the association between abnormal temporal artery and a subsequent diagnosis of GCA, showing odds ratios for each study, the pooled odds ratio, the weight of each study, and the 95% confidence interval.

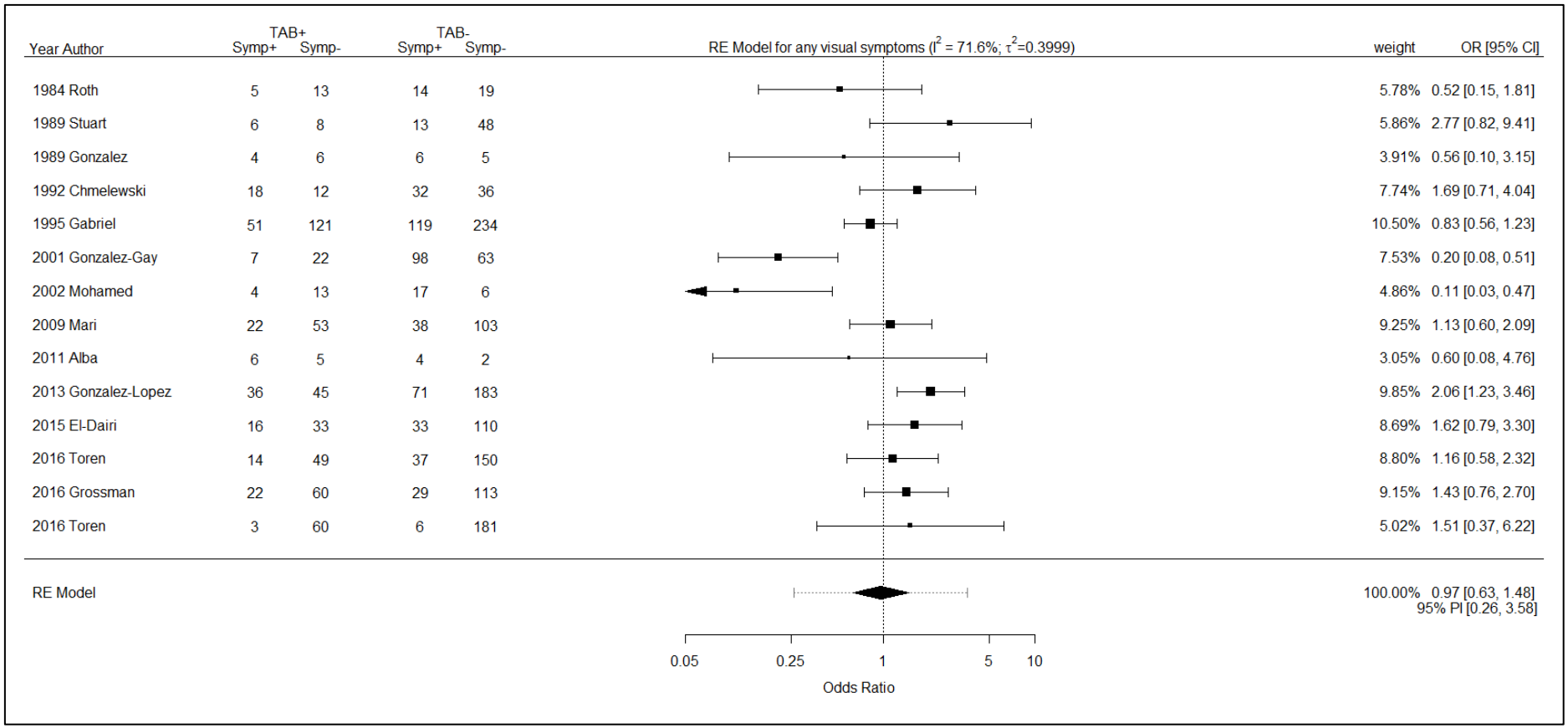

Figure 4: Forest plot of the association between visual impairment and a subsequent diagnosis of GCA, showing odds ratios for each study, the pooled odds ratio, the weight of each study, and the 95% confidence interval.

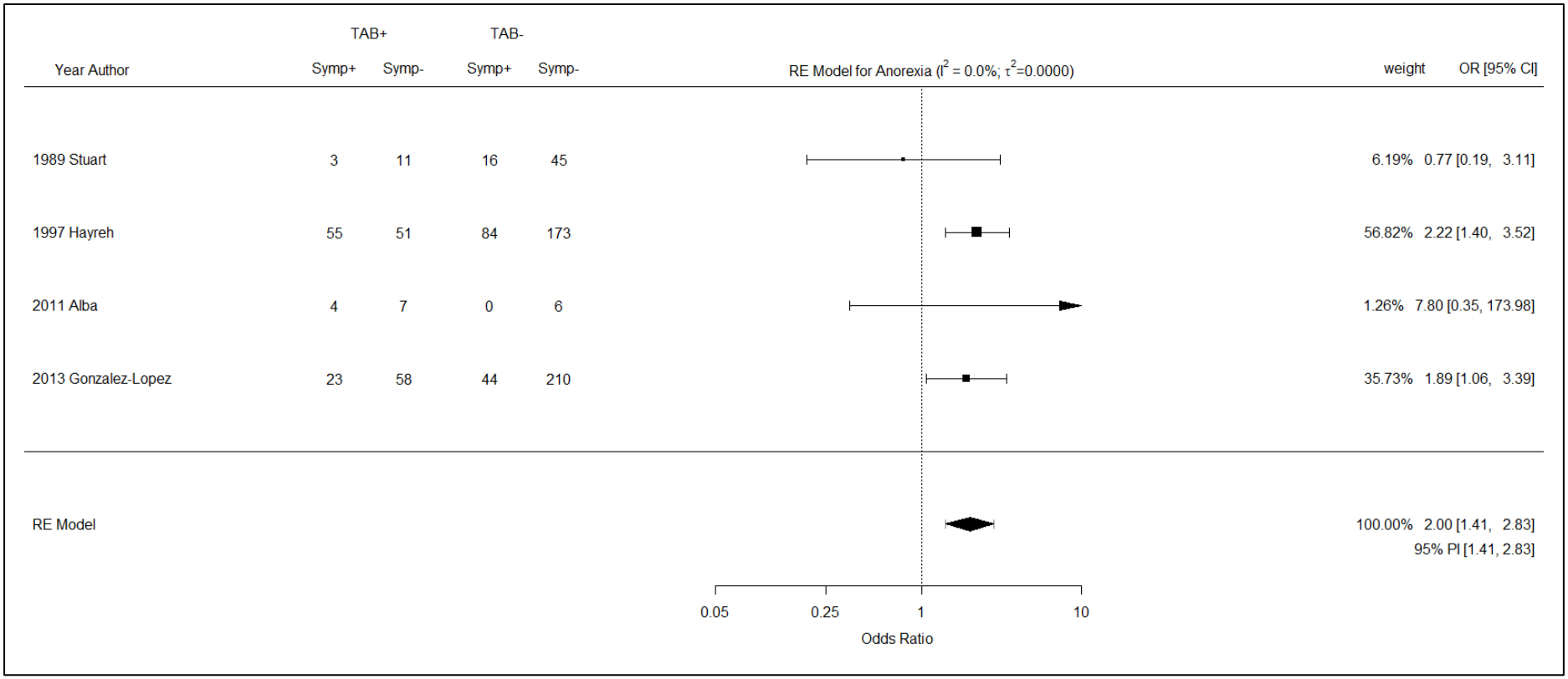

Figure 5: Forest plot of the association between anorexia and a subsequent diagnosis of GCA, showing odds ratios for each study, the pooled odds ratio, the weight of each study, and the 95% confidence interval.

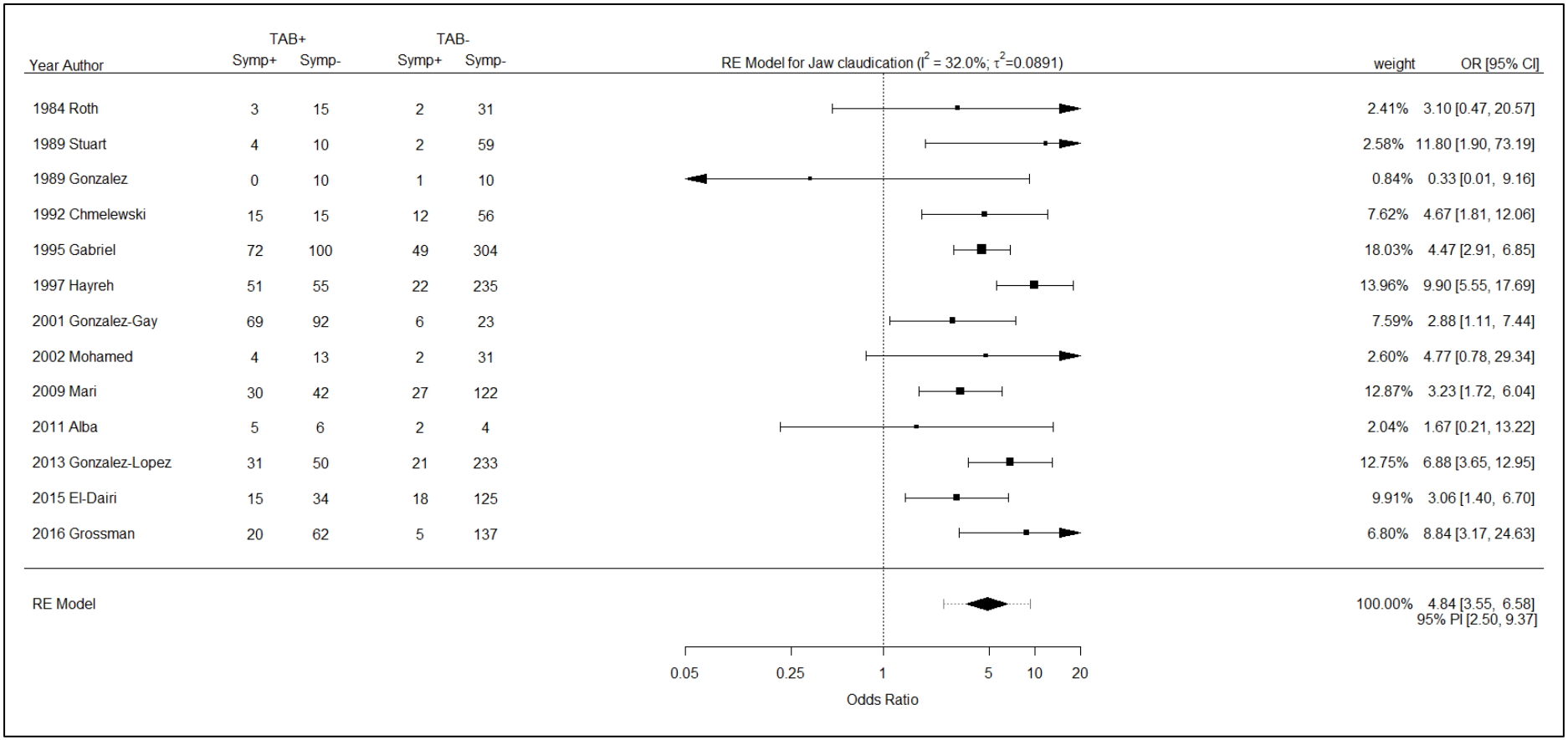

Figure 6: Forest plot of the association between jaw claudication and a subsequent diagnosis of GCA, showing odds ratios for each study, the pooled odds ratio, the weight of each study, and the 95% confidence interval.

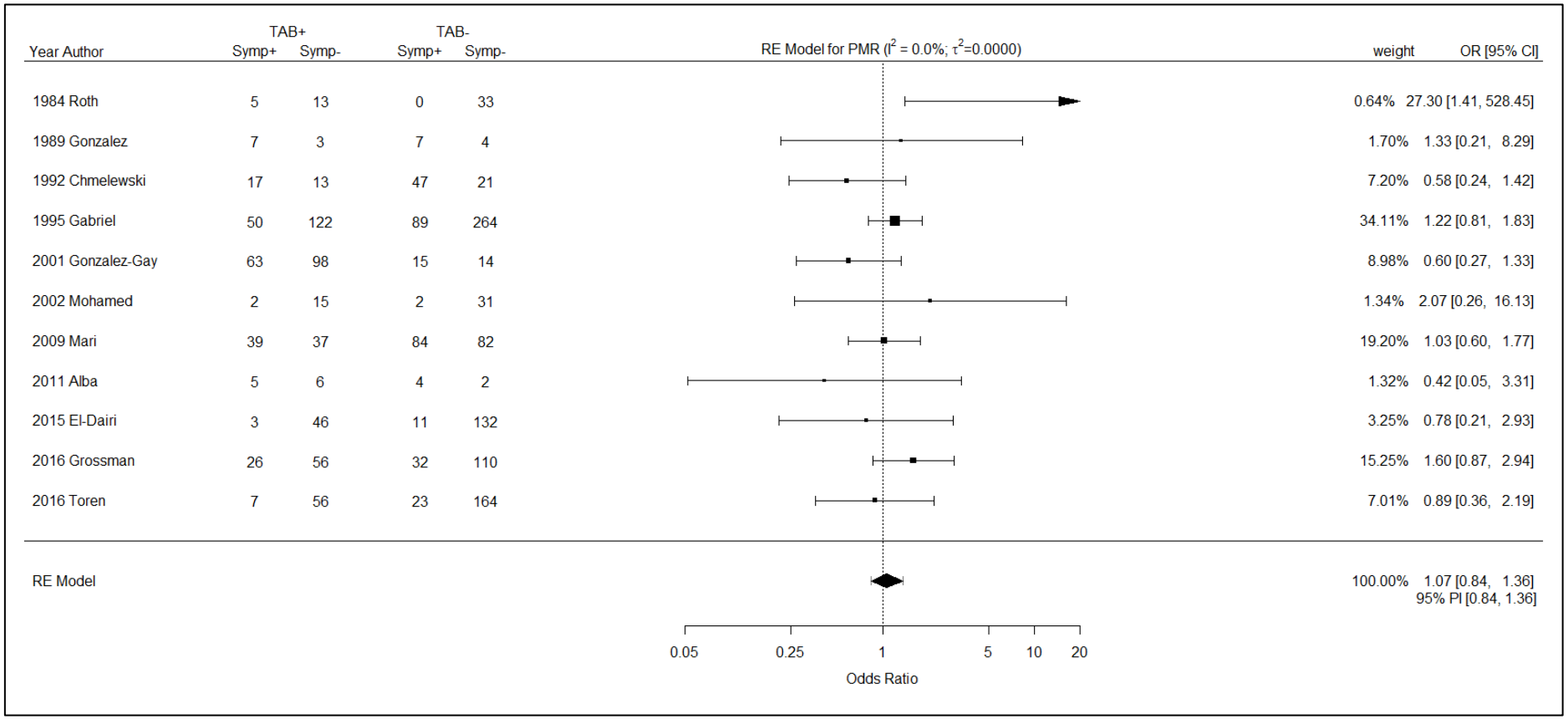

Figure 7: Forest plot of the association between PMR and a subsequent diagnosis of GCA, showing odds ratios for each study, the pooled odds ratio, the weight of each study, and the 95% confidence interval.

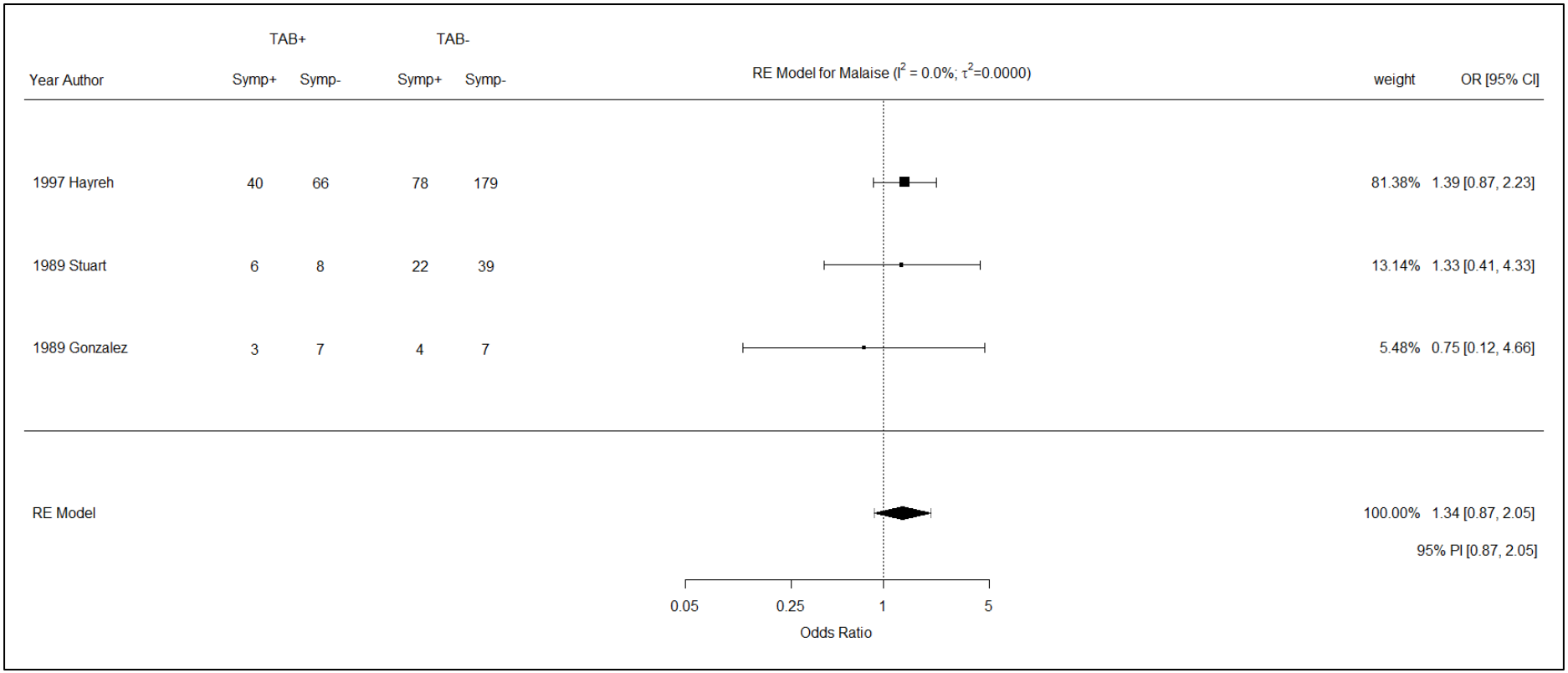

Figure 8: Forest plot of the association between Malaise and a subsequent diagnosis of GCA, showing odds ratios for each study, the pooled odds ratio, the weight of each study, and the 95% confidence interval.

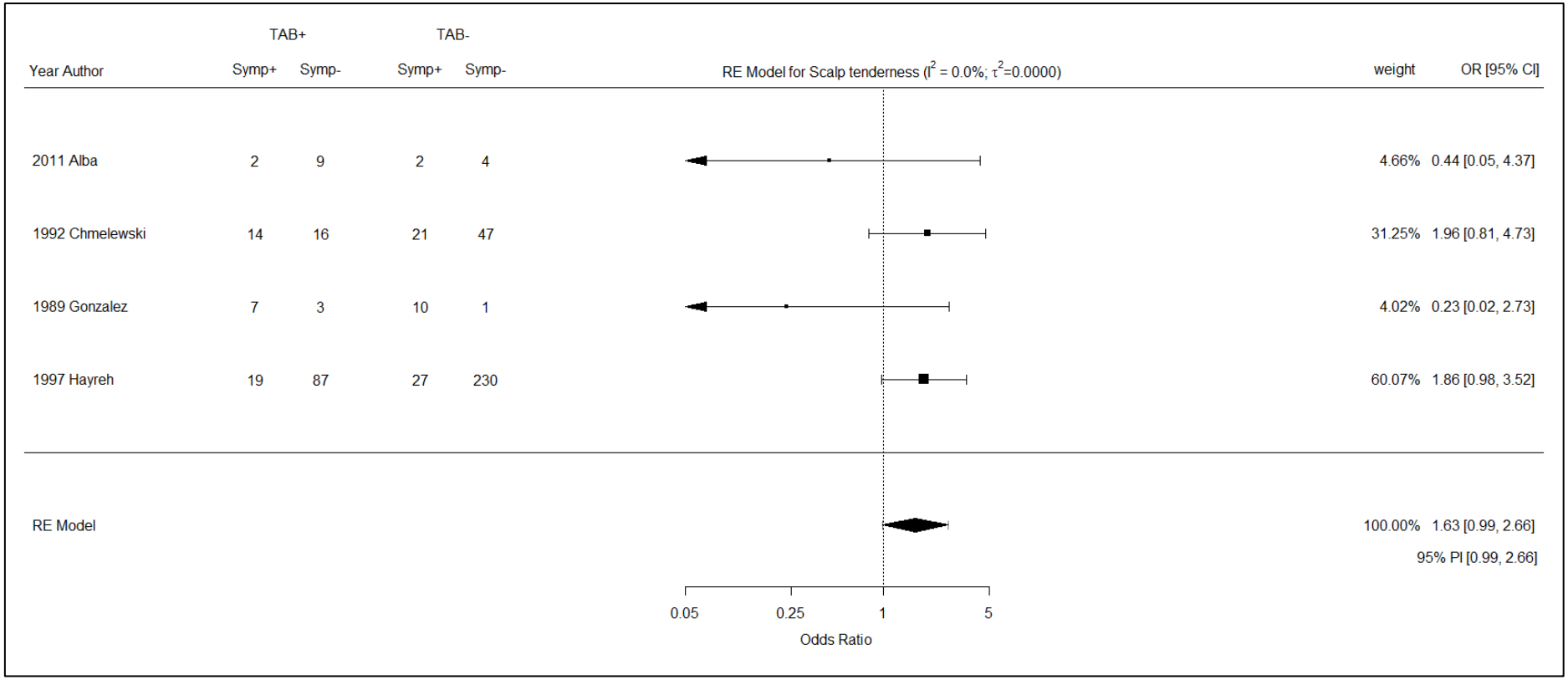

Figure 9: Forest plot of the association between scalp tenderness and a subsequent diagnosis of GCA, showing odds ratios for each study, the pooled odds ratio, the weight of each study, and the 95% confidence interval.

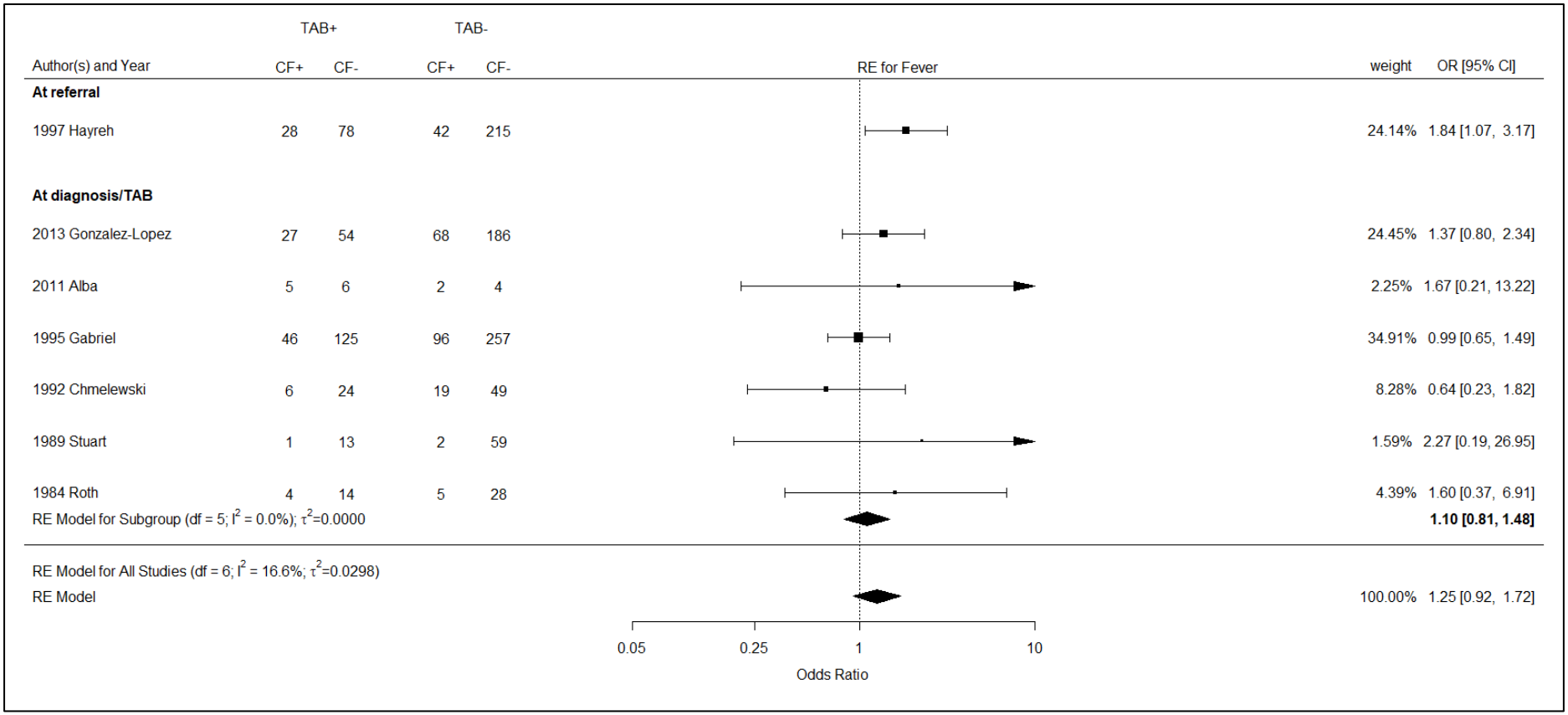

Figure 10: Forest plot of the association between fever and a subsequent diagnosis of GCA, showing odds ratios for each study, the pooled odds ratio, the weight of each study, and the 95% confidence interval.

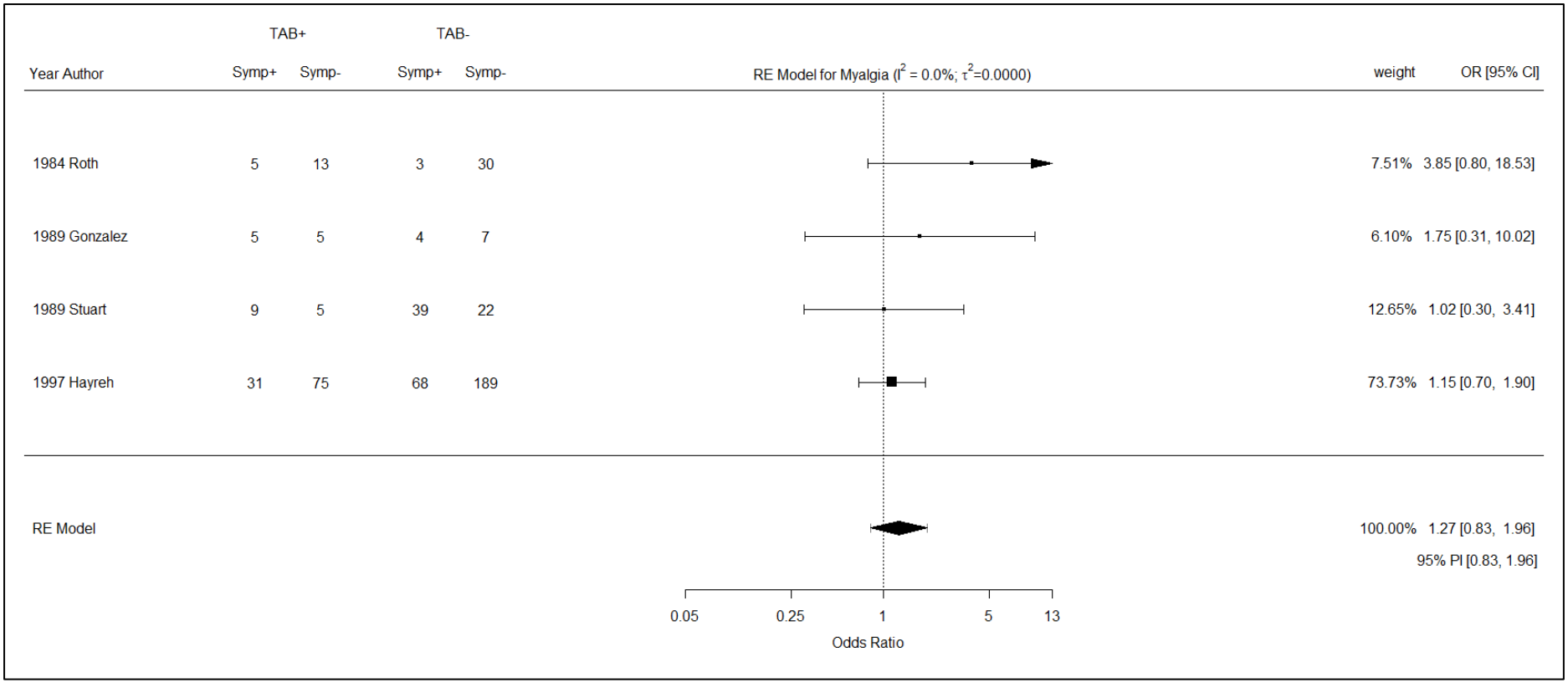

Figure 11: Forest plot of the association between myalgia and a subsequent diagnosis of GCA, showing odds ratios for each study, the pooled odds ratio, the weight of each study, and the 95% confidence interval.

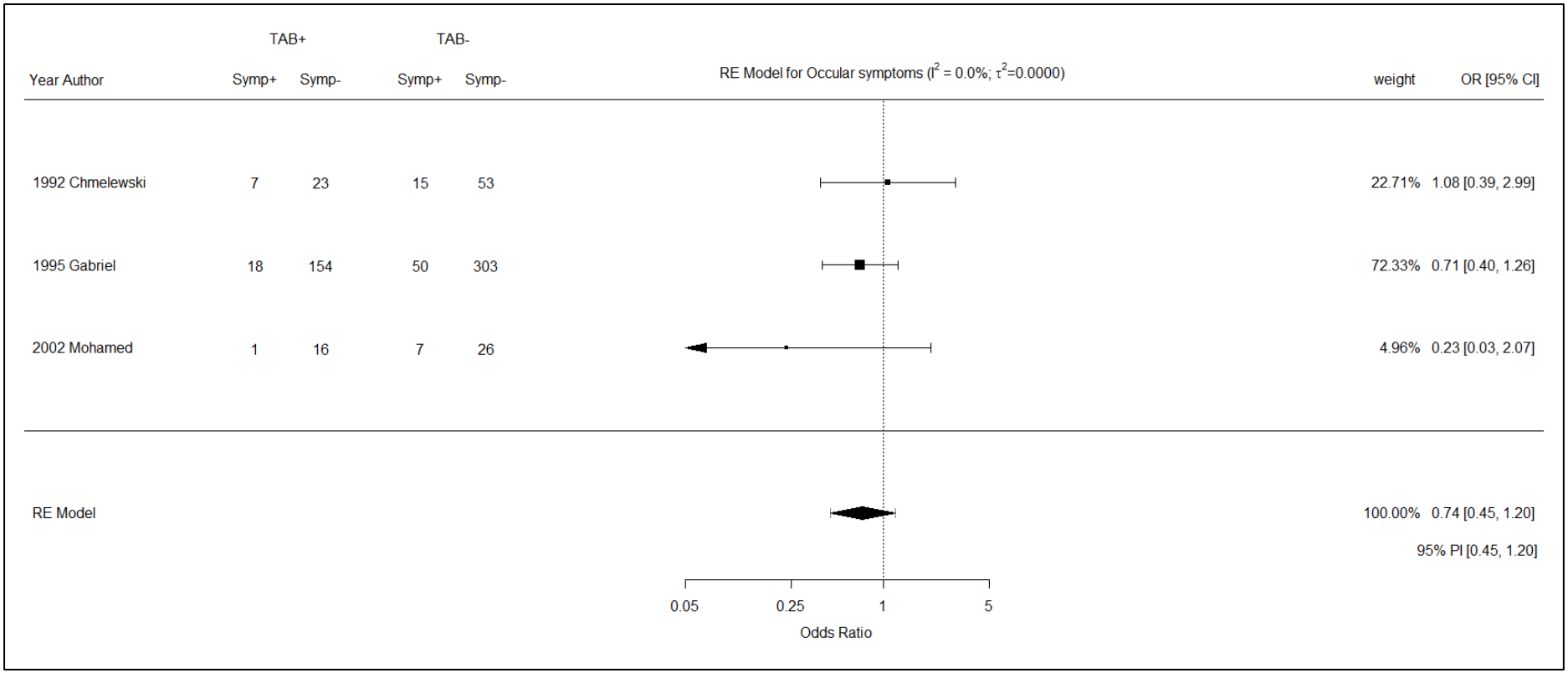

Figure 12: Forest plot of the association between ocular symptoms and a subsequent diagnosis of GCA, showing odds ratios for each study, the pooled odds ratio, the weight of each study, and the 95% confidence interval.

Appendix 3.8 – Subgroup association meta-analysis

Table 1: subgroup analysis for risk estimates

Clinical feature	**Duration**	**N**	**Pooled Odds Ratio**	**95% CI**	**I^2 (%)**	**τ^2**
Jaw claudication	At diagnosis/TAB	12	4.36	(3.41, 5.57)	0.0	0.00
Constitutional symptoms	At diagnosis/TAB	5	1.61	(0.75, 3.46)	74.0	0.51
Headache	At diagnosis/TAB	13	1.75	(1.11, 2.76)	73.1	0.43
Abnormal Temporal artery	At diagnosis/TAB	7	1.4	(0.49, 4.06)	90.9	1.70
Fever	At diagnosis/TAB	6	1.1	(0.81, 1.48)	0.0	0.00

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INDEPENDENT SCIENTIFIC ADVISORY COMMITTEE (ISAC) PROTOCOL APPLICATION FORM

PART 1: APPLICATION FORM

IMPORTANT

Both parts of this application must be completed in accordance with the guidance note 'Completion of the ISAC Protocol Application Form', which can be found on the CPRD website cprd.com/research-applications

FOR ISAC USE ONLY	
Protocol No. -	**Submission date -**

GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY

1. Study Title (Max. 255 characters)

Clinical features of giant cell arteritis (GCA): An observational study using linked electronic primary and secondary care medical records

2. Research Area (place '**X**' in all boxes that apply)

Drug Safety		Economics	
Drug Utilisation		Pharmacoeconomics	
Drug Effectiveness		Pharmacoepidemiology	
Disease Epidemiology	X	Methodological	
Health Services Delivery			

3. Chief Investigator

Title:	Dr
Full name:	James Prior
Job title:	Research Fellow
Affiliation/organisation:	Arthritis Research UK Primary Care Centre, Research Institute for Primary Care and Health Sciences, Keele University
Email address:	j.a.prior@keele.ac.uk
CV Number (if applicable):	037_18

4. Corresponding Applicant

Title:	Miss
Full name:	Lauren Barnett
Job title:	PhD student
Affiliation/organisation:	Arthritis Research UK Primary Care Centre, Research Institute for Primary Care and Health Sciences, Keele University
Email address:	l.barnett@keele.ac.uk
CV Number (if applicable):	

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5. List of all investigators/collaborators

Title:	Prof
Full name:	Kelvin Jordan
Job title:	Professor of Biostatistics
Affiliation/organisation:	Arthritis Research UK Primary Care Centre, Research Institute for Primary Care and Health Sciences, Keele University
Email address:	k.p.jordan@keele.ac.uk
CV Number (if applicable):	248_14CESL
Will this person be analysing the data? (Y/N)	N

Title:	Prof
Full name:	Christian Mallen
Job title:	iPCHS Director & NIHR Professor of General Practice
Affiliation/organisation:	Arthritis Research UK Primary Care Centre, Research Institute for Primary Care and Health Sciences (iPCHS), Keele University
Email address:	c.d.mallen@keele.ac.uk
CV Number (if applicable):	073_15CESP
Will this person be analysing the data? (Y/N)	N

Title:	Dr
Full name:	Alyshah Abdul-Sultan
Job title:	Honorary Senior Research Fellow
Affiliation/organisation:	Arthritis Research UK Primary Care Centre, Research Institute for Primary Care and Health Sciences (iPCHS), Keele University
Email address:	alyshah.sultan@hotmail.com
CV Number (if applicable):	14_191
Will this person be analysing the data? (Y/N)	N

Title:	Dr
Full name:	Toby Helliwell
Job title:	GP Researcher
Affiliation/organisation:	Arthritis Research UK Primary Care Centre, Research Institute for Primary Care and Health Sciences, Keele University
Email address:	t.helliwell@keele.ac.uk
CV Number (if applicable):	18-043R
Will this person be analysing the data? (Y/N)	N

[Add more investigators/collaborators as necessary by copy and pasting a new table for each investigator/collaborator]

6. Experience/expertise available

List below the member(s) of the research team who have experience with CPRD data.

Name:	Protocol Number/s:
Prof Kelvin Jordan	13_169; 13_135; 14_090; 15_140; 15_211; 17_181; 18_026
Dr Alyshah Abdul-Sultan	18_018R3
Dr James Prior	18_018R3

List below the member(s) of the research team who have statistical expertise.

Name(s):	

Prof Kelvin Jordan
Dr Alyshah Abdul-Sultan
Miss Lauren Barnett

List below the member(s) of the research team who have experience of handling large datasets (greater than 1 million records).

Name(s):
Prof Kelvin Jordan
Dr Alyshah Abdul-Sultan

List below the member(s) of the research team, or supporting the research team, who have experience of practicing in UK primary care.

Name(s):
Dr Toby Helliwell
Prof Christian Mallen

ACCESS TO THE DATA

7. Sponsor of the study

Institution/Organisation:	Keele University
Address:	Keele University, Keele, Staffs ST5 5BG

8. Funding source for the study

Same as Sponsor?	Yes	X	No	
Institution/Organisation:				
Address:				

9. Institution conducting the research

Same as Sponsor?	Yes	X	No	
Institution/Organisation:				
Address:				

10. Data Access Arrangements

Indicate with an '**X**' the method that will be used to access the data for this study:

Study-specific Dataset Agreement	

Institutional Multi-study Licence	X
Institution Name	Keele University
Institution Address	Keele University, ST5 5BG

Will the dataset be extracted by CPRD?

Yes		No	X

If yes, provide the reference number:

11. Data Processor(s):

Processing	X
Accessing	X

Storing	X	
Processing area (UK/EEA/Worldwide)		UK
Organisation name		Keele University
Organisation address		Keele University, Keele, Staffs ST5 5BG

Processing		
Accessing		
Storing		
Processing area (UK/EEA/Worldwide)		
Organisation name		
Organisation address		

[Add more processors as necessary by copy and pasting a new table for each processor]

INFORMATION ON DATA

12. Primary care data (place '**X**' in all boxes that apply)

CPRD GOLD	X	CPRD Aurum	X

13. Please select any linked data or data products being requested

Patient Level Data (place '**X**' in all boxes that apply)

ONS Death Registration Data		CPRD Mother Baby Link	
HES Admitted Patient Care	X	Pregnancy Register	
HES Outpatient		NCRAS (National Cancer Registration and Analysis Service) Cancer Registration Data	
HES Accident and Emergency		NCRAS Cancer Patient Experience Survey (CPES) data	
HES Diagnostic Imaging Dataset		NCRAS Systemic Anti-Cancer Treatment (SACT) data	
HES PROMS (Patient Reported Outcomes Measure)		NCRAS National Radiotherapy Dataset (RTDS) data	
		Mental Health Services Data Set (MHDS)	

Area Level Data (place '**X**' in all boxes that apply)

Practice level (UK)		**Patient level (England only)**	
Practice Level Index of Multiple Deprivation (Standard)		Patient Level Index of Multiple Deprivation	X
Practice Level Index of Multiple Deprivation (Non-standard)		Patient Level Townsend Score	
Practice Level Index of Multiple Deprivation Domains (Non-standard)			
Practice Level Carstairs Index for 2011 Census (Excluding Northern Ireland) (Standard)			
2011 Rural-Urban Classification at LSOA level (Non-standard)			

Reference number (where applicable):

14. Are you requesting linkage to a dataset not listed above?

Yes		No	X

If yes, provide the reference number:

15. Does any person named in this application already have access to any of these data in a patient identifiable form, or associated with an identifiable patient index?

Yes		No	X

If yes, provide further details:

VALIDATION/VERIFICATION

16. Does this protocol describe an observational study using purely CPRD data?

Yes	X	No	

17. Does this protocol involve requesting any additional information from GPs, or contact with patients?

Yes		No	X

If yes, provide the reference number:

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CPRD

PART 2: PROTOCOL INFORMATION

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*' and justification provided
A. Study Title (Max. 255 characters) Clinical features of giant cell arteritis (GCA): An observational study using linked electronic primary and secondary care medical records
B. Lay Summary (Max. 250 words) Giant cell arteritis (GCA) is a disease which causes swelling of blood vessels in the temple area and around the eyes. It affects people aged over 50 years and is most common in women between the ages of 70 and 80 years. A serious consequence of having GCA can be the sudden development of eyesight problems, which cannot be reversed but can be prevented if treatment is started early. Therefore, it is very important that GCA is identified as quickly as possible when it is suspected. General practitioners (GPs) are generally the first point of contact for healthcare in the UK. However, GCA remains difficult to identify and diagnose; firstly because GCA is a rare condition and secondly, because many symptoms related to GCA are also commonly seen in patients in this age group, for example, headaches. As a result of these factors, the diagnosis of GCA is commonly delayed and as a result, so too is treatment. The purpose of this study is to understand whether the number of people with GCA in the UK is changing over time and to identify clinical features and other health conditions which patients see their GP about which may be related to GCA, to help us improve diagnosing patients with GCA quicker, and more accurately.
C. Technical Summary (Max. 300 words) Giant cell arteritis (GCA) is the most common form of large/medium vessel vasculitis, typically affecting people over the age of 50 years. If untreated, it can lead to permanent visual loss. Diagnosing GCA is often difficult due to a wide range of non-specific presenting symptoms which can lead to delays in diagnosis and appropriate treatment. The overall aim of this study is to estimate the occurrence of GCA, and to identify the most common groups of clinical features presented prior to diagnosis. Our first objective is to estimate the burden of GCA in the UK population. The annual incidence and prevalence of GCA will be assessed between 1990 and 2017. Trends over time will be modelled using joinpoint regression. Our second objective is to examine the clinical features that patients present with in primary care prior to GCA diagnosis. We will perform a matched case-control study that will identify commonly reported clinical features (symptoms & comorbidities) prior to a GCA diagnosis. Using latent class analysis we will determine common patterns of clinical features presented to primary care prior to GCA diagnosis.
D. Outcomes to be Measured GCA diagnosis, Clinical features prior to a GCA diagnosis

E. Objectives, Specific Aims and Rationale

The objective of this project is to estimate the occurrence of GCA in the UK and to assess whether there are groups of clinical features that are more indicative of a diagnosis.

Specific aims include;

1. To examine the incidence and prevalence of GCA in the UK population and assess how these have changed over time.
2. To measure the frequency of clinical features presenting to primary care prior to GCA diagnosis and their association with GCA.
3. To identify common combinations (patterns) of clinical features that patients present with prior to a GCA diagnosis.

Rationale

Given the rarity of GCA and non-specific symptoms that patients may present with related to GCA, the diagnosis of GCA by clinicians is often delayed. Thus, a better understanding of the clinical features which patients' experience prior to diagnosis may help reduce diagnostic delay (Prior et al., 2017). The UK population is ageing, hence there are more people at risk of a GCA diagnosis than there was at the time of the previous study on incidence by Petri et al (2015) which examined data up to 2011.

F. Study Background

Giant cell arteritis (GCA) is the most common form of medium and large vessel vasculitis. GCA typically affects people over the age of 50 years (Smeeth, Cook, & Hall, 2006), with incidence peaking between 70 and 80 years, and typically affecting more women than men (Petri, Nevitt, Sarsour, Napalkov, & Collinson, 2015; Salvarani, Cantini, & Hunder, 2008).

The most commonly reported GCA symptoms are any headache, fever, weight loss, and visual disturbances including diplopia (double vision) and blurred vision (Smetana & Shmerling, 2002). However, the number of patients reporting common symptoms vary largely between studies. Other reported symptoms are arthralgia/myalgia and fatigue (Smetana & Shmerling, 2002), which are common in this population and can also be connected to other conditions, making it more difficult for them to be connected to a rare condition such as GCA. The only method of confirming a GCA diagnosis is to conduct a temporal artery biopsy (TAB), which is conducted in secondary care in the UK.

Amongst TAB confirmed cases of GCA, the proportion of patients reporting headache ranges from 52.4% to 92.9% (Duhaut et al., 1999; Toren et al., 2016). Reporting of visual disturbances in biopsy proven GCA cases can range from 30% to 60% (Chmelewski, McKnight, Kevin, Agudelo, & Wise, 1992; Gabriel, O'Fallon, Achkar, Lie, & Hunder, 1995). The reported presence of comorbidities in patients prior to their GCA diagnosis is also inconsistent. Peripheral arthritis has been reported in 11% of GCA patients pre-diagnosis in one study (Narvaez et al., 2003), but in only 3% in another (Zenone & Puget, 2013). Common comorbidities pre-diagnosis, such as cardiovascular diseases, and diabetes, show the same inconsistency between studies ranging between 4% and 22% for cardiovascular disease (Sun, Ma, Zheng, Tian, & Zeng, 2016; Unizony et al., 2017); and 5% and 37% for diabetes (Espitia et al., 2012; Pugnet, Sailler, Bourrel, Montastruc, & LapeyreMestre, 2015). Such varied presentation and heterogeneity of prevalence estimates of common clinical features (symptoms and comorbidities) in a rarely seen condition makes diagnosing GCA difficult in primary care.

When suspected, diagnosis of GCA in primary care often uses the American College of Rheumatology (ACR) classification criteria (Hunder et al., 1990). This includes 5 criteria that were developed to identify GCA from other forms of vasculitis (Hunder et al., 1990). The 5 criteria include the age of the patient, if they are newly presenting with a headache, if they have an elevated erythrocyte sedimentation rate (ESR), if they have temporal artery abnormality, and an abnormal biopsy result (Hunder et al., 1990). However, this is a classification, rather than diagnostic tool and therefore has limited ability in identifying new cases of GCA, furthermore, these criteria do not include other symptoms that GCA patients can present with such as fever or visual complications. As stated previously the proportion of GCA patients presenting with headache is varied and can be as little as 52%. Therefore, the ACR criteria is not suitable for use as a diagnostic tool. Currently, there is no validated diagnostic tool for GCA, thereby making it more difficult in primary care to conclusively diagnose a patient. Temporal artery biopsies are used to confirm diagnosis, but these are conducted in secondary care.

In the UK, GCA is typically managed in primary care once diagnosis has been confirmed and treatment has been stabilised. The most common treatment for GCA are glucocorticoids for example prednisolone, which works by supressing part of the immune system, thereby reducing inflammation (NHS, 2018). A prompt diagnosis of GCA can be challenging for GPs since there are a multitude of symptoms connected to the disease (Petri et al., 2015; Smetana & Shmerling, 2002). As a result, this diagnostic delay can result in treatment delay, which can influence the outcomes of GCA patients (Patil et al., 2015). Though prednisolone is an effective treatment for GCA, this cannot reverse the loss of sight if established, which can be prevented in patients with GCA who are treated appropriately.

GCA is a relatively rare condition, with GPs unlikely to see more than 1 new case a year (Helliwell et al., 2018). There have been two previous studies in the UK on incidence and prevalence of GCA (Petri et al., 2015; Smeeth et al., 2006) using CPRD. However, the latest study (Petri et al., 2015) was conducted on data that is now 7 years old and did not stratify by year, instead giving an overall incidence estimate of GCA for 2000 to 2011. As a result, there was no information on the trend pattern of GCA incidence in the UK population. It is essential for policy makers to have up-to-date estimates of the incidence and prevalence of GCA so that the health care interventions and guidelines can be tailored accordingly. Modelling the trends in the population over more than two decades will show whether incidence of the disease is changing, or is stable, further providing essential information on the possible burden to healthcare.

As part of a wider body of work related to this submission, we have conducted a systematic review examining the prevalence of clinical features present in patients prior to GCA diagnosis. Forty-three relevant studies were identified for the final review and meta-analysis. All 43 were set in secondary care and had small sample sizes of less than 100. No article undertook an analysis adjusted for key covariates, such as demographic information, to quantify the association between the presenting features and a GCA diagnosis. The review found that headache (pooled prevalence 77%), elevated ESR (76%), and systemic symptoms, such as weight loss, fever, asthenia, etc., had the highest prevalences in GCA patients prior to diagnosis. Headache was recorded in 35 articles in the review, and was the most commonly recorded symptom. Elevated ESR and systemic symptoms were recorded in less than 10 articles each. Systemic symptoms have a high prevalence in patients prior to their GCA diagnosis, but also present an area of difficulty regarding diagnosis as they are all common symptoms that can be linked to other more common conditions if presented with independently.

Due to these contrasting presentations of clinical features, delay in achieving a prompt diagnosis of GCA is common. A systematic review found that the average diagnostic delay for GCA patients was 9 weeks, and longer if they did not present with cranial symptoms such as headache (Prior et al., 2017).

GCA is a rare disease that is difficult to identify due to non-specific presenting features. If not identified and treated quickly patients can be at risk of permanent visual loss. Studies that have investigated presenting features of GCA patients used small samples, set within secondary care, and undertook no formal statistical analysis to quantify the

relationship between presenting features and a GCA diagnosis, whilst adjusting for other factors such as patient demographics. In the UK GCA is treated in primary care where it has proven difficult to identify. Therefore, it is important that a study is undertaken to identify common patterns of presenting features so as to help reduce diagnostic delay. The only way to do this is in the UK is to use a national electronic health records database, such as CPRD, where symptoms, comorbidities, demographic information, amongst others, are all recorded.

G. Study Type

The first aim of this study is to model the incidence and prevalence of GCA in the UK population. This will be completed using a descriptive design.
The second and third aims will be hypothesis testing studies as they will examine the association between clinical features presented with in primary care and a subsequent GCA diagnosis.

H. Study Design

Case-control. GCA cases will be identified within CPRD, in comparison to a population group without GCA.

I. Feasibility counts

Previous studies using similar data (Petri et al., 2015; Smeeth et al., 2006) identified 4,000 incident cases of the disease between 1990 and 2001, and 5,000 between 2000 and 2011. Based on this, we estimate there will be at least 12,000+ incident GCA cases between 1990 and 2017.

J. Sample size considerations

We will determine the annual prevalence with a 95% confidence level with expected margin of error of less than ±0.05% given an expected annual prevalence of 0.25%.
For aims 2 & 3, we anticipate >12,000 cases of GCA to be defined in our time period, and each case will have 5 matched controls, giving a total sample size of 72,000. The null hypothesis for our study is that the odds ratio for a symptom be equal to one; that is, it has no predictive value for a GCA diagnosis. In the scenario of 80% power, with 5% significance, a matching ratio of 1:5 cases to controls, and the prevalence of the symptom occurring in the control population to be 30%, we would require a total sample size of 2,208 (368 cases) to detect an odds ratio of 1.4. Increasing the power to 90%, but holding all other assumptions, we would require a sample size of 2,970 (495 cases).

K. Planned use of linked data (if applicable):

To better ascertain pre-existing clinical features, we will request hospital episode statistics to be used in a sensitivity analysis.

L. Definition of the Study population

For our first aim, as per Smeeth et al (Smeeth et al., 2006) our study population will include all individuals aged over 40 years and registered within CPRD between 1990 and 2017 inclusive. Only patients contributing data within the up-to-standard (UTS) period will be included. To calculate point prevalence, our denominator will include all registered patients within CPRD who are alive and contributing data on 31st December 2017. For our incidence rate analysis, we will only include patients registered within CPRD at any time between 1990 and 2017 with no history of GCA before the study start date. Cases and person-time within the first 2 years of patient registration with the practice will be excluded to avoid inclusion of prevalent cases. The study start date will be defined as the latest of: 1st of January 1990, up-to-standard date, date patient turned 40, and patient current registration date + 2 years. The study end date will be defined as the earliest of: 1st of January 2018 transferred out date, date of death, event date, and the last date of data collection from practice.

To quantify the association between recorded clinical features and a subsequent GCA diagnosis, we will identify incident GCA cases matched to five controls without GCA (on year of birth, gender, and practice). Each case will be assigned an index date corresponding to the date of GCA diagnosis. Controls will be assigned the same index date as their matched GCA case.

For aims 2 & 3, those with less than 2 years registration prior to index date will be excluded. To better ascertain clinical features we will conduct a subgroup analyses using HES-CPRD linked data restricted to cases with index date at least 2 years after start point of HES collection (1st April 1997).

M. Selection of comparison group(s) or controls

Eligible controls will have no recorded diagnosis of GCA in their records, but will satisfy all other eligibility criteria detailed in section L. We will only match controls on gender, year of birth, and practice.

N. Exposures, Outcomes and Covariates

GCA definition: patients aged 40 years or over, and who have a first diagnosis of GCA entered into their medical record whilst registered with a practice contributing to CPRD during the study period. The Read codes used to identify a GCA diagnosis can be seen in **Appendix 1**.

GCA diagnosis has been validated within CPRD in a previous study with high accuracy, with 91% of GCA cases correctly identified (Smeeth et al., 2006), therefore Read code lists are a suitable way to identify incident GCA cases. However, to further improve sensitivity of our case definition, we will undertake additional sensitivity analyses and restrict our cases to those prescribed 2 or more oral glucocorticoid prescriptions after their GCA diagnosis; one in the first 6 months, and a second within six months of the date of the first prescription (Unizony et al., 2017).

Clinical features definition: A list of clinical features (symptoms and comorbidities) likely to be associated with GCA prior to diagnosis have been identified by our previous systematic review and meta-analysis. We will include any of these identified clinical features if they appear in a patient's record up to 2 years prior to the GCA diagnosis. We will use the 24 clinical features identified from the meta-analysis (in progress) in our study (**Table 1**).

All clinical features will be defined using Read codes. A list of Read codes used to identify the aforementioned clinical features can be seen in **Appendix 2**.

Table 1: List of the most commonly reported clinical features taken from the literature review.

Clinical feature	Raised ESR
Jaw claudication	Ischaemic optic neuropathy
Anorexia	Arthralgia/Myalgia
Headache	Polymyalgia rheumatica (PMR)
Fever	Cardiovascular diseases – arterial hypertension, coronary artery disease, congestive heart failure.
Fatigue/Malaise	Transient ischaemic attacks
Any visual impairment	Atrial fibrillation
Hypertension	Myocardial infarction
Asthenia	Stroke
Weight loss	Cancer - any
Infection - Urinary tract, viral.	Cough
Peripheral arthritis	Scalp tenderness
Diabetes	Depression
Anxiety	

Covariates: Consultation frequency (number of consultations per year), most recent prior to index date of smoking status, alcohol consumption, socio-economic status, and the most recent measure of Body Mass Index (BMI) will be used. BMI will be categorised according to the World Health Organisation (WHO) grouping of underweight (<18.5Kg/m^2), normal (18.5-25Kg/m^2), overweight (25-29.9Kg/m^2) or obese (≥30Kg/m^2), and also used as a continuous variable.

Smoking status will be categorised as current, never, or ex-smokers. For alcohol consumption we will use information extracted on units per week. Those in the "never" group will have consumed 0 units per week, the "light drinker" group will have consumed between 1-7, the "moderate drinker" group will have consumed between 8-14, and those classed as "heavy drinker" will consume >15 units per week.

Socio-economic status will be defined using the patient-level Index of Multiple Deprivation, split at quintile score, where 1 is most deprived, and 5 is least deprived. This will be used only for the sensitivity analysis given it is not available for everyone.

O. Data/ Statistical Analysis

Aim 1

We will calculate crude incidence rate of GCA by dividing the total number of new cases by the total person-years of follow-up at risk. We will stratify incidence by age, gender, geographical region, and calendar year. We will use Poisson regression model to assess the impact of covariates (age, gender, and region) on the incidence of GCA. Joinpoint regression (Institute, 2017) will be used to determine changes in trends over time in the incidence of GCA. We will stratify consultation prevalence by year. The numerator will be the total number of GCA cases (incident and prevalent) consulting per year, and the denominator will be the number of patients within CPRD on 31st December of the same year and who are alive and contributing data. We will determine crude and age-gender standardised incidence and prevalence estimates (direct standardisation to the UK 2017 age and gender population structure).

Aim 2

In order to calculate estimates for the association between a clinical feature and a GCA diagnosis, we will fit conditional logistic regression models, which will produce Odds Ratios (OR), and 95% Confidence intervals (CI). The model will be adjusted for the covariates detailed in section N, and robust variance estimators to account for the clustering within general practices.

Aim 3

Only features found to have a statistical and clinical (by review of research team) significance with a GCA diagnosis from aim 2 will be included in the analysis for aim 3. To identify clusters of clinical features in the 2 years prior to a diagnosis we will use latent class analysis (LCA) in cases (patients with GCA). A one cluster model will be fitted initially which will assume that all GCA patients experience the same pattern of clinical features prior to diagnosis, and then repeated up to an eight-cluster model. Models will be compared using the Bayesian Information Criterion (BIC) where the lowest value indicates the best fitting model, and the Lo-Mendell-Rubin likelihood ratio test, to test for appropriate number of classes. Patient posterior probabilities (PP) for allocating patients to clusters will be identified and the mean PP will be used to measure cluster separation. A mean PP of more than 0.7 indicates that patients are distinctly classified into clusters. In sensitivity analyses we will adjust the number of years prior to a GCA diagnosis to be used for investigation up to a maximum of 5 years. Assessment and interpretation of the clusters will be conducted by the research team. We will use multinomial logistic regression to determine covariates (listed in section N) associated with clusters derived from the final model.

Sensitivity analysis

Sensitivity analyses will include altering the definition of how we identify GCA cases within CPRD. This will involve broadening the GCA definition to include those with a prescription for corticosteroids along with a Read code. Our main analysis will include all practices contributing to CPRD and define clinical features using only CPRD primary care information. In sensitivity analysis, we will restrict analysis to practices consenting to linkage to HES

and deprivation in order to expand our definition of comorbidities to include those recorded within HES, and adjust for neighbourhood deprivation.

P. Plan for addressing confounding

We will adjust for confounding factors in the analysis stage as variables in the logistic regression. These include BMI, alcohol consumption, socio-economic status and smoking habits.

Unmeasured confounding is an acknowledged limitation in medical record studies. During dissemination of the project we will acknowledge this as an overall limitation of our study. We will compare between clusters (aim 3) on the covariates.

Q. Plans for addressing missing data

Based on our previous work, we anticipate that around 25%, 7% and 23% of patients will have missing information on BMI, smoking status and alcohol consumption, respectively. Firstly, we will conduct a complete case analysis. Secondly the missing data will be considered as a separate category in a missing indicator methodological approach (Pedersen et al., 2017).

We will also use multiple imputation for BMI, as patients' weight is likely to satisfy the missing at random assumption (Marston et al., 2010); however alcohol and smoking are not. By using multiple imputation, we can compare estimates from different missing data methodologies.

R. Patient or user group involvement (if applicable)

Public and patient involvement was conducted during the proposal for funding by one of the research team (AAS). The protocol and aims reflect this involvement.

S. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

Results of this study will be published in peer-reviewed journals and presented at appropriate conferences, such as the international society of clinical Biostatistics (ISCB), British Society for Rheumatology (BSR), and the PhD thesis.

Conflict of interest statement:
The authors' state there is no conflict of interest, financial or otherwise, with respect to this work; they have full access to all of the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis.

T. Limitations of the study design, data sources, and analytic methods

The main limitation of this study is whether the diagnosis of GCA is correct. Patients with suspected GCA are often identified in general practice and referred to secondary care to confirm diagnosis. However Smeeth et al. (Smeeth et al., 2006) carried out external validation of GCA cases in CPRD and reported 91% of cases coded with a GCA diagnosis was supported.

Another potential limitation is the ascertainment of clinical features prior to a GCA diagnosis. The proposed list will be drawn from our systematic review; however, this may not include all possible features that are associated with the disease, either due to the large variation surrounding their prevalence in GCA patients, or their absence in CPRD records, such as laboratory results (e.g. ESR, biopsy results). However, CPRD is proven to be a high-quality database, which only includes data taken from practices that have up-to-standard data.

An acknowledged limitation of our study is unmeasured confounding, which is an inevitable disadvantage to medical record research where only the variables in the data are available to be included in the analysis.

Amendment – 31/10/2019

We no longer intend to use the Aurum database for this study, and will only be conducting the analysis outlines in this protocol on GOLD.

We no longer intend to use the Hospital of Episode Statistics (HES), and the sensitivity population definition and analyses detailed in sections L and O will no longer be conducted.

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List of Appendices

Appendix 1: List of Read codes for GCA diagnosis

Appendix 2: List of Read codes for included clinical features pre-diagnosis

Appendix 4.2 – Code lists for clinical features and glucocorticoids

Table 1: Read code lists for clinical features

Medcode	**Read Term**
Headache	
83480	History of headache
29394	Headache character NOS
21663	Bilateral headache
129	Headache
3340	Temporal headache
5767	C/O - a headache
9915	Headache character
1788	Occipital headache
9891	Generalised headache
11321	Unilateral headache
130	Frontal headache
9048	Parietal headache
1197	[D]Headache
95330	[X]Vascular headache, not elsewhere classified
Fever	
46292	O/E - fever NOS
6065	Fever symptoms

17989	[D] Fever of unknown origin
14744	O/E - fever - general
66310	O/E - fever - continuous
1020	[D] Fever NOS
5892	O/E - fever
35761	O/E - fever - general NOS
106211	H/O: fever
22444	[D]Persistent fever
31412	O/E – fever – intermittent
107717	O/E – fever – irregular
Weight loss/Anorexia	
654	Weight decreasing
4663	Abnormal weight loss
5812	Abnormal weight loss - symptom
102563	Unintentional weight loss
12398	Complaining of weight loss
29029	O/E -weight 10-20% below ideal
126	O/E - Underweight
24496	Body mass index less than 20
3647	[D]Abnormal loss of weight
12530	[D]Underweight
53746	[D] Anorexia – NOS
7608	Appetite loss – anorexia

912	[D] Anorexia
Visual impairment	
6499	Visual symptoms
105665	moderate visual impairment, binocular
105493	moderate visual impairment, monocular
104666	mild or no visual impairment, binocular
104853	severe visual impairment, binocular
Medcode	**Read Term**
55436	both eyes total visual impairment
108199	visual impairment
105206	severe visual impairment, monocular
18462	Diplopia (double vision)
1617	Diplopia
5991	Diplopia/Double vision
34686	refractive diplopia
104077	Blindness, monocular
3851	Blindness, one eye, unspecified
47956	Blindness both eyes NOS
98637	[X] Visual disturbances and blindness
1990	Blindness, both eyes
55108	Unspecified blindness both eyes
105202	H/O Amaurosis Fugax
1195	Aumaurosis Fugax

Fatigue	
6242	Fatigue – symptom
23932	[D] Malaise and fatigue NOS
1688	[D] Fatigue
44215	[D] Malaise and fatigue
5583	Lethargy - symptom
5794	Tiredness symptom
1404	Fatigue
7235	Tired all the time
5751	Tired all the time
17736	Malaise/lethargy
9220	Exhaustion
97140	Activity management for chronic fatigue syndrome
29292	Tiredness symptom NOS
3361	Neurasthenia - nervous debility
16561	[X]Neurasthenia
4546	Chronic fatigue syndrome
1688	[D]Fatigue
1371	[D]Lethargy
1147	[D]Tiredness
5814	[D]Lassitude
23932	[D]Malaise and fatigue NOS

Recorded hypertension	
204	Hypertensive disease
8732	BP - hypertensive disease
799	Essential hypertension
351	High blood pressure
107704	Primary hypertension
15377	Malignant essential hypertension
1894	Benign essential hypertension
4372	Systolic hypertension
83473	Diastolic hypertension
10818	Essential hypertension NOS
3712	Hypertension NOS
16292	Hypertensive heart disease
50157	Malignant hypertensive heart disease
Medcode	**Read Term**
95334	Malignant hypertensive heart disease without CCF
72668	Malignant hypertensive heart disease with CCF
103046	Malignant hypertensive heart disease NOS
52427	Benign hypertensive heart disease

61660	Benign hypertensive heart disease without CCF
52127	Benign hypertensive heart disease with CCF
105938	Benign hypertensive heart disease NOS
31464	Hypertensive heart disease NOS
61166	Hypertensive heart disease NOS without CCF
8857	Cardiomegaly - hypertensive
62718	Hypertensive heart disease NOS with CCF
16173	Hypertensive heart disease NOS
4668	Hypertensive renal disease
17434	Nephrosclerosis
39649	Malignant hypertensive renal disease
43935	Benign hypertensive renal disease
32423	Hypertensive renal disease with renal failure
15106	Hypertensive renal disease NOS
29310	Renal hypertension
63466	Hypertensive heart and renal disease
67232	Malignant hypertensive heart and renal disease
63000	Benign hypertensive heart and renal disease

21837	Hypertensive heart&renal dis wth (congestive) heart failure
28684	Hypertensive heart and renal disease with renal failure
57987	Hyperten heart&renal dis+both(congestv)heart and renal fail
68659	Hypertensive heart and renal disease NOS
7329	Secondary hypertension
31755	Secondary malignant hypertension
59383	Secondary malignant renovascular hypertension
73293	Secondary malignant hypertension NOS
57288	Secondary benign hypertension
25371	Secondary benign renovascular hypertension
51635	Secondary benign hypertension NOS
34744	Hypertension secondary to endocrine disorders
16059	Secondary hypertension NOS
31387	Secondary renovascular hypertension NOS
31341	Hypertension secondary to drug
42229	Secondary hypertension NOS

105371	Stage 1 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
105316	Stage 1 hypertension
108136	Stage 1 hyperten (NICE 2011) without evidnce end organ damge
109797	Stage 1 hyperten (NICE 2011) with evidnce end organ damge
105989	Severe hypertension (Nat Inst for Health Clinical Ex 2011)
105487	Severe hypertension
Medcode	**Read Term**
105480	Hypertension resistant to drug therapy
105274	Stage 2 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
18765	Other specified hypertensive disease
7057	Hypertensive disease NOS
18482	Hypertension six month review
19070	Hypertension annual review
102406	Hypertension 9 month review
Cardiovascular/Cerebrovascular conditions	
7783	ECG: myocardial infarction
26975	ECG: antero-septal infarct.
26972	ECG:posterior/inferior infarct

55401	ECG: subendocardial infarct
52705	ECG: lateral infarction
59032	ECG: myocardial infarct NOS
61670	Diab mellit insulin-glucose infus acute myocardial infarct
764	Acute rheumatic fever
48189	Rheumatic fever without heart involvement
44756	Rheumatic fever with heart involvement
24636	Acute rheumatic pericarditis
36886	Acute rheumatic endocarditis
48099	Acute rheumatic myocarditis
73540	Other acute rheumatic heart disease
23619	Acute rheumatic pancarditis
105615	Other acute rheumatic heart disease NOS
68849	Acute rheumatic heart disease NOS
5326	Rheumatic chorea
20246	Sydenham's chorea
69995	Rheumatic chorea with heart involvement
63252	Rheumatic chorea without mention of heart involvement
72936	Rheumatic chorea NOS
59942	Other specified acute rheumatic fever
14840	Acute rheumatic fever NOS

9312	Chronic rheumatic heart disease
44376	Chronic rheumatic pericarditis
40957	Adherent rheumatic pericardium
72628	Chronic rheumatic myopericarditis
1267	Mitral valve diseases
16545	Rheumatic mitral valve disease
1885	Mitral stenosis
32435	Rheumatic mitral stenosis
51879	Rheumatic mitral insufficiency
21807	Mitral incompetence - rheumatic
22837	Mitral regurgitation - rheumatic
44488	Mitral stenosis with insufficiency
50983	Mitral stenosis with incompetence
44328	Mitral stenosis with regurgitation
28662	Nonrheumatic mitral valve stenosis
57633	Ruptured mitral valve cusp
30443	Mitral valve disease NOS
18100	Rheumatic aortic valve disease
Medcode	**Read Term**
9391	Rheumatic aortic stenosis
32211	Rheumatic aortic insufficiency
43347	Aortic incompetence - rheumatic
7963	Aortic regurgitation - rheumatic

63960	Rheumatic aortic stenosis with insufficiency
50809	Rheumatic aortic valve disease NOS
10078	Diseases of mitral and aortic valves
8274	Mitral and aortic stenosis
49355	Mitral stenosis and aortic insufficiency
61250	Mitral stenosis and aortic incompetence
17596	Mitral stenosis and aortic regurgitation
33262	Mitral insufficiency and aortic stenosis
31759	Mitral incompetence and aortic stenosis
33907	Mitral regurgitation and aortic stenosis
31727	Mitral and aortic incompetence
94872	Mitral and aortic insufficiency
11878	Mitral and aortic regurgitation
70698	Multiple mitral and aortic valve involvement
29158	Mitral and aortic valve disease NOS
68126	Other chronic rheumatic endocardial disease
16373	Tricuspid valve disease NEC
31505	Rheumatic tricuspid stenosis
60266	Rheumatic tricuspid insufficiency
21980	Tricuspid regurgitation - rheumatic
42239	Tricuspid incompetence - rheumatic

93114	Rheumatic tricuspid stenosis and insufficiency
93113	Rheumatic tricuspid stenosis and regurgitation
62186	Rheumatic tricuspid stenosis and incompetence
56029	Tricuspid stenosis, cause unspecified
42128	Tricuspid insufficiency, cause unspecified
34869	Tricuspid incompetence, cause unspecified
9286	Tricuspid regurgitation, cause unspecified
72306	Tricuspid stenosis and insufficiency, cause unspecified
49551	Tricuspid stenosis and regurgitation, cause unspecified
72613	Rheumatic tricuspid valve disease NOS
44167	Rheumatic pulmonary valve disease
62207	Rheumatic pulmonary stenosis
54088	Rheumatic pulmonary insufficiency
105626	Rheumatic pulmonary stenosis and insufficiency
36768	Rheumatic pulmonary valve disease NOS
15132	Rheumatic endocarditis NOS
59275	Rheumatic valvulitis, chronic NOS

15643	Other specified chronic rheumatic heart disease
62404	Rheumatic myocarditis
57980	Other and unspecified rheumatic heart disease
53878	Rheumatic heart disease unspecified
22262	Rheumatic left ventricular failure
59854	Other rheumatic heart disease NOS
20001	Chronic rheumatic heart disease NOS
240	Ischaemic heart disease
Medcode	**Read Term**
24783	Arteriosclerotic heart disease
20416	Atherosclerotic heart disease
1792	IHD - Ischaemic heart disease
241	Acute myocardial infarction
13566	Attack - heart
2491	Coronary thrombosis
30421	Cardiac rupture following myocardial infarction (MI)
1677	MI - acute myocardial infarction
13571	Thrombosis - coronary
17689	Silent myocardial infarction
12139	Acute anterolateral infarction

5387	Other specified anterior myocardial infarction
40429	Acute anteroapical infarction
17872	Acute anteroseptal infarction
14897	Anterior myocardial infarction NOS
8935	Acute inferolateral infarction
29643	Acute inferoposterior infarction
23892	Posterior myocardial infarction NOS
14898	Lateral myocardial infarction NOS
63467	True posterior myocardial infarction
3704	Acute subendocardial infarction
9507	Acute non-Q wave infarction
10562	Acute non-ST segment elevation myocardial infarction
1678	Inferior myocardial infarction NOS
30330	Acute Q-wave infarct
17133	Mural thrombosis
32854	Acute posterolateral myocardial infarction
29758	Acute transmural myocardial infarction of unspecif site
12229	Acute ST segment elevation myocardial infarction
34803	Other acute myocardial infarction

28736	Acute atrial infarction
62626	Acute papillary muscle infarction
41221	Acute septal infarction
46017	Other acute myocardial infarction NOS
14658	Acute myocardial infarction NOS
27951	Other acute and subacute ischaemic heart disease
23579	Postmyocardial infarction syndrome
15661	Dressler's syndrome
36523	Preinfarction syndrome
4656	Crescendo angina
39655	Impending infarction
1431	Unstable angina
19655	Angina at rest
61072	Myocardial infarction aborted
55137	MI - myocardial infarction aborted
7347	Unstable angina
17307	Angina at rest
34328	Refractory angina
Medcode	**Read Term**
18118	Worsening angina
11983	Acute coronary syndrome
54251	Preinfarction syndrome NOS

39449	Coronary thrombosis not resulting in myocardial infarction
9413	Other acute and subacute ischaemic heart disease
9276	Acute coronary insufficiency
68357	Microinfarction of heart
39693	Subendocardial ischaemia
21844	Transient myocardial ischaemia
27977	Other acute and subacute ischaemic heart disease NOS
1430	Angina pectoris
20095	Angina decubitus
18125	Nocturnal angina
29902	Angina decubitus NOS
12986	Prinzmetal's angina
11048	Variant angina pectoris
36854	Coronary artery spasm
25842	Angina pectoris NOS
66388	Status anginosus
54535	Stenocardia
7696	Syncope anginosa
1414	Angina on effort
32450	Ischaemic chest pain

9555	Post infarct angina
26863	New onset angina
12804	Stable angina
28554	Angina pectoris NOS
28138	Other chronic ischaemic heart disease
5413	Coronary atherosclerosis
1655	Triple vessel disease of the heart
1344	Coronary artery disease
3999	Single coronary vessel disease
5254	Double coronary vessel disease
6331	Aneurysm of heart
27484	Cardiac aneurysm
2155	Ventricular cardiac aneurysm
67087	Other cardiac wall aneurysm
105250	Mural cardiac aneurysm
59193	Aneurysm of coronary vessels
91774	Acquired atrioventricular fistula of heart
41677	Aneurysm of heart NOS
36609	Atherosclerotic cardiovascular disease
7320	Ischaemic cardiomyopathy
29421	Silent myocardial ischaemia
34633	Other specified chronic ischaemic heart disease

24540	Chronic coronary insufficiency
23078	Chronic myocardial ischaemia
35713	Other specified chronic ischaemic heart disease NOS
15754	Other chronic ischaemic heart disease NOS
Medcode	**Read Term**
18842	Subsequent myocardial infarction
45809	Subsequent myocardial infarction of anterior wall
38609	Subsequent myocardial infarction of inferior wall
72562	Subsequent myocardial infarction of other sites
46166	Subsequent myocardial infarction of unspecified site
36423	Certain current complication follow acute myocardial infarct
24126	Haemopericardium/current comp folow acut myocard infarct
23708	Atrial septal defect/curr comp folow acut myocardal infarct
37657	Ventric septal defect/curr comp fol acut myocardal infarctn

59189	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
59940	Ruptur chordae tendinae/curr comp fol acute myocard infarct
69474	Rupture papillary muscle/curr comp fol acute myocard infarct
29553	Thrombosis atrium,auric append&vent/curr comp foll acute MI
8568	Cardiac syndrome X
32272	Postoperative myocardial infarction
46112	Postoperative transmural myocardial infarction anterior wall
46276	Postoperative transmural myocardial infarction inferior wall
106812	Postoperative transmural myocardial infarction unspec site
41835	Postoperative subendocardial myocardial infarction
68748	Postoperative myocardial infarction, unspecified
105479	Coronary microvascular disease
22383	Other specified ischaemic heart disease
1676	Ischaemic heart disease NOS

7180	Pulmonary circulation diseases
22412	Heart disease - pulmonary
63217	Acute pulmonary heart disease
8464	Acute cor pulmonale
1266	Pulmonary embolism
24444	Infarction - pulmonary
9701	Pulmonary embolus
18121	Post operative pulmonary embolus
96209	Recurrent pulmonary embolism
4717	Pulmonary infarct
65533	Acute pulmonary heart disease NOS
46294	Chronic pulmonary heart disease
245	Primary pulmonary hypertension
42901	Kyphoscoliotic heart disease
Medcode	**Read Term**
54113	Other chronic pulmonary heart disease
34065	Secondary pulmonary hypertension
102444	Thromboembolic pulmonary hypertension
71046	Other chronic pulmonary heart disease NOS
15782	Chronic pulmonary heart disease NOS
5695	Chronic cor pulmonale
24549	Other pulmonary circulation disease
31883	Pulmonary vessel disease

53377	Arteriovenous fistula of pulmonary vessels
22781	Aneurysm of pulmonary artery
65954	Other specified pulmonary circulation disease
37807	Pulmonary arteritis
51540	Pulmonary vessel rupture
41728	Other specified pulmonary circulation disease NOS
73599	Other pulmonary circulation disease NOS
61138	Other specified pulmonary circulation disease
16084	Pulmonary circulation disease NOS
30171	Other forms of heart disease
41527	Acute myocarditis NOS
33673	Conduction disorders
19191	Conduction disorders of heart
4549	Heart block
3810	Complete atrioventricular block
24377	Third degree atrioventricular block
3603	Partial atrioventricular block
58032	Atrioventricular block unspecified
12149	First degree atrioventricular block
46992	Prolonged P-R interval

10922	Mobitz type II atrioventricular block
27928	Mobitz type I (Wenckebach) atrioventricular block
103752	Mobitz type 1 second degree atrioventricular block
36629	Second degree atrioventricular block
27375	Atrioventricular block NOS
7482	Left bundle branch hemiblock
17840	Left bundle branch block
62349	Left anterior fascicular block
69809	Left posterior fascicular block
53826	Left bundle branch hemiblock NOS
26318	Left main stem bundle branch block
9906	Right bundle branch block
18117	Other bundle branch block
3032	Bundle branch block unspecified
98675	Right BBB with left posterior fascicular block
57069	Right BBB with left anterior fascicular block
72653	Other bilateral bundle branch block
10712	Trifascicular block
17206	Bifascicular block
39003	Other bundle branch block NOS

39843	Other heart block
18437	Sinoatrial block
Medcode	**Read Term**
54554	Interventricular block NOS
35947	Right fascicular block
46178	Other heart block NOS
25147	Anomalous atrioventricular excitation
50788	Accelerated atrioventricular conduction
69216	Accessory atrioventricular conduction
72888	Pre-excitation atrioventricular conduction
32059	Ventricular pre-excitation
8230	Wolff-Parkinson-White syndrome
42803	Anomalous atrioventricular excitation NOS
27874	Other conduction disorders
34326	Lown-Ganong-Levine syndrome
5714	Atrioventricular dissociation
22691	Romano - Ward syndrome
39956	Jervell and Lange-Nielsen syndrome
65653	Right fascicular block
19337	Long Q-T syndrome
101485	Pacemaker twiddler's syndrome
65073	Other conduction disorders NOS
44096	Conduction disorders unspecified

3769	Stokes-Adams syndrome
36227	Conduction disorders NOS
4044	Cardiac dysrhythmias
6503	Cardiac arrhythmias
4940	Paroxysmal supraventricular tachycardia
1297	Paroxysmal atrial tachycardia
23647	Paroxysmal atrioventricular tachycardia
51845	Paroxysmal junctional tachycardia
29491	Paroxysmal nodal tachycardia
35124	Paroxysmal supraventricular tachycardia NOS
3418	Paroxysmal ventricular tachycardia
7794	Ventricular tachycardia
25266	Paroxysmal tachycardia unspecified
60047	Essential paroxysmal tachycardia
70366	Bouveret-Hoffmann syndrome
1381	Paroxysmal tachycardia NOS
2212	Atrial fibrillation and flutter
1664	Atrial fibrillation
1757	Atrial flutter
1268	Paroxysmal atrial fibrillation
35127	Non-rheumatic atrial fibrillation
96277	Permanent atrial fibrillation

96076	Persistent atrial fibrillation
107472	Paroxysmal atrial flutter
111876	
112181	
111893	
23437	Atrial fibrillation and flutter NOS
4374	Ventricular fibrillation and flutter
4827	Ventricular fibrillation
25583	Cardiac arrest-ventricular fibrillation
5484	Ventricular flutter
41916	Ventricular fibrillation and flutter NOS
Medcode	**Read Term**
2099	Cardiac arrest
25407	Cardio-respiratory arrest
33402	Asystole
33899	Cardiac arrest with successful resuscitation
51140	Electromechanical dissociation with successful resuscitation
7630	Electromechanical dissociation
49882	Cardiac arrest, unspecified
7457	Ectopic beats
3909	Premature beats
2249	Ectopic beats unspecified

2579	Extrasystoles
19979	Supraventricular ectopic beats
4802	Ventricular ectopic beats
9023	Atrial premature depolarization
29654	Junctional premature depolarization
31809	Ventricular premature depolarization
27413	Ectopic beats NOS
426	Sinus arrhythmia
109821	Atrial standstill
7827	Other cardiac dysrhythmias
27463	Pulsus alternans
9563	Pulse missed beats
4772	Skipped beat
4421	Heart beats irregular
3849	Persistent sinus bradycardia
18268	Severe sinus bradycardia
95919	Brugada syndrome
5576	Sick sinus syndrome
7410	Sinoatrial node dysfunction NOS
23494	Wandering atrial pacemaker
8651	Nodal rhythm disorder
7005	Sinus tachycardia
9515	Bigeminal pulse

1536	Supraventricular tachycardia NOS
31690	Re-entry ventricular arrhythmia
31133	Other cardiac dysrhythmia NOS
1535	Cardiac dysrhythmia NOS
2062	Heart failure
2906	Congestive cardiac failure
10079	Right heart failure
10154	Right ventricular failure
9524	Biventricular failure
23707	Acute congestive heart failure
32671	Chronic congestive heart failure
27884	Decompensated cardiac failure
11424	Compensated cardiac failure
94870	Congestive heart failure due to valvular disease
884	Left ventricular failure
23481	Asthma - cardiac
43618	Pulmonary oedema - acute
5942	Impaired left ventricular function
5255	Acute left ventricular failure
Medcode	**Read Term**
27964	Acute heart failure
101138	Heart failure with normal ejection fraction

106897	Heart failure with preserved ejection fraction
104275	Right ventricular failure
4024	Heart failure NOS
12590	Weak heart
17278	Cardiac failure NOS
36193	Other specified heart disease
59687	Other ill-defined heart disease
41179	Other ill-defined heart disease NOS
1811	Other heart disease NOS
1490	Heart disease NOS
107462	Rheumatic heart disease
107591	Carditis due to rheumatic fever
52517	[X]Ischaemic heart diseases
39546	[X]Other forms of angina pectoris
47637	[X]Other forms of chronic ischaemic heart disease
96838	[X]Acute transmural myocardial infarction of unspecif site
109035	[X]Subsequent myocardial infarction of other sites
68401	[X]Other forms of acute ischaemic heart disease

99991	[X]Subsequent myocardial infarction of unspecified site
1204	Heart attack
1223	Cardiac failure
101137	HFNEF - heart failure with normal ejection fraction
398	Congestive heart failure
22672	Cardiovascular disease, unspecified
10444	H/O: cardiovascular disease
73901	[X] Cerebrovascular diseases
1469	Stroke and cerebrovascular accident unspecified
6116	CVA – cerebrovascular accident unspecified
2790	Peripheral neuropathy
1664	Atrial fibrillation
241	Acute myocardial infarction
1677	MI – acute myocardial infarction
48980	Cardiovascular disease annual review
18686	Stroke/CVA annual review
Elevated ESR	
14924	ESR raised
46	Erythrocyte sedimentation rate
27037	Erythrocyte sediment rate NOS

273	Erythrocyte sedimentation rate
Anxiety/Depression	
131	Anxiousness
29569	Tenseness
3881	Agitated
11890	C/O - panic attack
Medcode	**Read Term**
462	Panic attack
6408	[X] Panic attack
13124	O/E - anxious
93401	Anxious
19000	O/E - panic attack
636	Anxiety states
1907	Phobic disorders
11940	Acute panic state due to acute stress reaction
15220	[X]Persistant anxiety depression
7749	[X]Mild anxiety depression
9386	[X]Phobic anxiety disorders
5385	[X]Other anxiety disorders
1996	Depressed
9796	Symptoms of depression
10015	Depressed mood

1908	O/E - depressed
12399	Depression annual review
10610	Single major depressive episode
4639	[X]Depressive episode
9211	[X]Moderate depressive episode
11717	[X]Mild depressive episode
15099	Recurrent major depressive episode
10825	Seasonal affective disorder
27491	Atypical depressive disorder
9183	Masked depression
1055	Agitated depression
5879	Agitated depression
655	Anxiety with depression
1533	Brief depressive reaction
36246	Brief depressive reaction NOS
16632	Prolonged depressive reaction
324	Depressive disorder NEC
5726	[X]Mood - affective disorders
4639	[X]Depressive episode
3292	[X]Recurrent depressive disorder
42857	[X]Persistent mood affective disorders
7953	[X]Dysthymia

50243	[X]Other persistent mood affective disorders
39767	[X]Persistent mood affective disorder, unspecified
28008	[X]Other mood affective disorders
37090	[X]Unspecified mood affective disorder
11913	[X]Mixed anxiety and depressive disorder
32845	[X]Depressive conduct disorder
PMR & Arthralgia/Myalgia	
1408	Polymyalgia rheumatica
29472	Polymyalgia with GCA
5864	Pain in joint – arthralgia
202	Arthralgia of unspecified site
1418	Arthralgia of multiple joints
29775	Arthralgia NOS
1338	Myalgia unspecified
Diabetes	
13070	Initial diabetic assessment
Medcode	**Read Term**
7563	Diabetic on diet only
1684	Diabetic on oral treatment
8842	Diabetic on insulin
13068	Last hypo. attack

13281	Frequency of hypo. attacks
31752	Frequency of hospital treated hypoglycaemia
40363	Frequency of GP or paramedic treated hypoglycaemia
13069	Has seen dietician - diabetes
38078	Understands diet - diabetes
25636	Diabetic diet - poor compliance
20696	Injection sites - diabetic
22823	Diabetic foot examination
10977	Diabetic peripheral neuropathy screening
18583	Hypoglycaemic attack requiring 3rd party assistance
13196	Fundoscopy - diabetic check
90301	Insulin needles changed daily
53238	Diabetic drug side effects
66274	Insulin needles changed for each injection
16490	Diabetic treatment changed
11047	Conversion to insulin
107331	Conversion to insulin in secondary care
107508	Conversion to insulin by diabetes specialist nurse

109700	Conversion to non-insulin injectable medication
13071	Diabetic - good control
69152	Insulin needles changed less than once a day
2378	Diabetic - poor control
9013	Unstable diabetes
22959	Chronic hyperglycaemia
2478	Brittle diabetes
21420	Loss of hypoglycaemic warning
37625	Recurrent severe hypos
108218	Hypoglycaemic warning absent
22023	Diabetic - poor control NOS
43951	Diabetic - cooperative patient
17869	Diabetic-uncooperative patient
83485	Insulin dose changed
29041	Date diabetic treatment start
55123	Date diabetic treatment stopp.
96010	Insulin treatment initiated
12506	Diabetes: practice programme
12675	Diabetes: shared care programme
95994	Diabetic foot screen

100533	Unsuitable for diabetes year of care programme
101190	Declined consent for diabetes year of care programme
8836	Diabetes management plan given
100791	Insulin treatment stopped
101728	Diabetic on subcutaneous treatment
12307	Diabetes care by hospital only
Medcode	**Read Term**
28769	Diabetic on insulin and oral treatment
102490	Diabetic assessment of erectile dysfunction
50175	Diabetic foot risk assessment
102549	Insulin dose
46577	Diabetes: shared care in pregnancy - diabetol and obstet
103847	Checking accuracy of blood glucose meter
26604	Diabetic diet - good compliance
26605	Attended diabetes structured education programme
51066	Family/carer attended diabetes structured education prog
35383	Diabetic patient unsuitable for digital retinal photography

93530	Attended DESMOND structured programme
94186	Diabetes structured education programme completed
94011	Attended XPERT diabetes structured education programme
93390	Attended DAFNE diabetes structured education programme
93491	DAFNE diabetes structured education programme completed
93529	DESMOND diabetes structured education programme completed
93631	XPERT diabetes structured education programme completed
93854	Diabetes structured education programme declined
711	Diabetes mellitus
38986	Diabetes mellitus with no mention of complication
24490	Diabetes mellitus, juvenile type, no mention of complication
1038	Insulin dependent diabetes mellitus

14803	Diabetes mellitus, adult onset, no mention of complication
14889	Maturity onset diabetes
506	Non-insulin dependent diabetes mellitus
50972	Diabetes mellitus NOS with no mention of complication
1682	Diabetes mellitus with ketoacidosis
53200	Diabetes mellitus, juvenile type, with ketoacidosis
54856	Diabetes mellitus, adult onset, with ketoacidosis
38617	Other specified diabetes mellitus with ketoacidosis
42505	Diabetes mellitus NOS with ketoacidosis
21482	Diabetes mellitus with hyperosmolar coma
40023	Diabetes mellitus, juvenile type, with hyperosmolar coma
43139	Diabetes mellitus, adult onset, with hyperosmolar coma
Medcode	**Read Term**
72345	Diabetes mellitus NOS with hyperosmolar coma
15690	Diabetes mellitus with ketoacidotic coma

42567	Diabetes mellitus, juvenile type, with ketoacidotic coma
68843	Diabetes mellitus, adult onset, with ketoacidotic coma
59288	Other specified diabetes mellitus with coma
65062	Diabetes mellitus NOS with ketoacidotic coma
16502	Diabetes mellitus with renal manifestation
2475	Diabetic nephropathy
93922	Diabetes mellitus, juvenile type, with renal manifestation
35105	Diabetes mellitus, adult onset, with renal manifestation
13279	Other specified diabetes mellitus with renal complications
35107	Diabetes mellitus with nephropathy NOS
33254	Diabetes mellitus with ophthalmic manifestation
6125	Diabetic annual review
41389	Diabetes mellitus, adult onset, + ophthalmic manifestation
47377	Other specified diabetes mellitus with ophthalmic complicatn

34283	Diabetes mellitus NOS with ophthalmic manifestation
16230	Diabetes mellitus with neurological manifestation
59903	Diabetic amyotrophy
7795	Diabetes mellitus with neuropathy
16491	Diabetes mellitus with polyneuropathy
39317	Diabetes mellitus, adult onset, + neurological manifestation
61523	Other specified diabetes mellitus with neurological comps
22573	Diabetes mellitus NOS with neurological manifestation
35399	Diabetes mellitus with peripheral circulatory disorder
32403	Diabetes mellitus with gangrene
32556	Diabetes with gangrene
63357	Diabetes mellitus, adult, + peripheral circulatory disorder
33807	Diabetes mellitus, adult with gangrene
69124	IDDM with peripheral circulatory disorder
56803	NIDDM with peripheral circulatory disorder

112402	Other specified diabetes mellitus with periph circ comps
65025	Diabetes mellitus NOS with peripheral circulatory disorder
1647	Insulin dependent diabetes mellitus
18505	IDDM-Insulin dependent diabetes mellitus
Medcode	**Read Term**
46963	Insulin-dependent diabetes mellitus with renal complications
49276	Insulin-dependent diabetes mellitus with ophthalmic comps
52283	Insulin-dependent diabetes mellitus with neurological comps
52104	Insulin dependent diabetes mellitus with multiple complicatn
26855	Unstable insulin dependent diabetes mellitus
44443	Insulin dependent diabetes mellitus with ulcer
60499	Insulin dependent diabetes mellitus with gangrene

6509	Insulin dependent diabetes mellitus with retinopathy
6791	Insulin dependent diabetes mellitus - poor control
31310	Insulin dependent diabetes maturity onset
56448	Insulin-dependent diabetes without complication
24694	Insulin dependent diabetes mellitus with mononeuropathy
41716	Insulin dependent diabetes mellitus with polyneuropathy
57621	Insulin dependent diabetes mellitus with nephropathy
44440	Insulin dependent diabetes mellitus with hypoglycaemic coma
44260	Insulin dependent diabetes mellitus with diabetic cataract
64446	Insulin dependent diab mell with peripheral angiopathy
65616	Insulin dependent diabetes mellitus with arthropathy
39809	Insulin dependent diab mell with neuropathic arthropathy

46290	Other specified diabetes mellitus with multiple comps
64449	Unspecified diabetes mellitus with multiple complications
4513	Non-insulin dependent diabetes mellitus
5884	NIDDM - Non-insulin dependent diabetes mellitus
	Type 2 diabetes mellitus
18219	Type II diabetes mellitus
52303	Non-insulin-dependent diabetes mellitus with renal comps
50225	Type II diabetes mellitus with renal complications
18209	Type 2 diabetes mellitus with renal complications
50429	Non-insulin-dependent diabetes mellitus with ophthalm comps
59725	Type II diabetes mellitus with ophthalmic complications
Medcode	**Read Term**
70316	Type 2 diabetes mellitus with ophthalmic complications

55842	Non-insulin-dependent diabetes mellitus with neuro comps
67905	Type II diabetes mellitus with neurological complications
45919	Type 2 diabetes mellitus with neurological complications
62146	Non-insulin-dependent diabetes mellitus with multiple comps
108005	Type 2 diabetes mellitus with multiple complications
34912	Non-insulin dependent diabetes mellitus with ulcer
55075	Type II diabetes mellitus with ulcer
65704	Type 2 diabetes mellitus with ulcer
40401	Non-insulin dependent diabetes mellitus with gangrene
62107	Type II diabetes mellitus with gangrene
46150	Type 2 diabetes mellitus with gangrene
17262	Non-insulin-dependent diabetes mellitus with retinopathy
58604	Type II diabetes mellitus with retinopathy
42762	Type 2 diabetes mellitus with retinopathy

8403	Non-insulin dependent diabetes mellitus - poor control
24458	Type II diabetes mellitus - poor control
45913	Type 2 diabetes mellitus - poor control
29979	Non-insulin-dependent diabetes mellitus without complication
109103	Type II diabetes mellitus without complication
105784	Type 2 diabetes mellitus without complication
72320	Non-insulin dependent diabetes mellitus with mononeuropathy
50813	Type II diabetes mellitus with mononeuropathy
45467	Non-insulin dependent diabetes mellitus with polyneuropathy
47409	Type II diabetes mellitus with polyneuropathy
109865	Type 2 diabetes mellitus with polyneuropathy
59365	Non-insulin dependent diabetes mellitus with nephropathy
64571	Type II diabetes mellitus with nephropathy

24836	Type 2 diabetes mellitus with nephropathy
43785	Non-insulin dependent diabetes mellitus with hypoglyca coma
56268	Type II diabetes mellitus with hypoglycaemic coma
61071	Type 2 diabetes mellitus with hypoglycaemic coma
69278	Non-insulin depend diabetes mellitus with diabetic cataract
48192	Type II diabetes mellitus with diabetic cataract
44779	Type 2 diabetes mellitus with diabetic cataract
Medcode	**Read Term**
54212	Non-insulin-dependent d m with peripheral angiopath
54899	Type II diabetes mellitus with peripheral angiopathy
60699	Type 2 diabetes mellitus with peripheral angiopathy
24693	Non-insulin dependent diabetes mellitus with arthropathy
18143	Type II diabetes mellitus with arthropathy

49869	Type 2 diabetes mellitus with arthropathy
40962	Non-insulin dependent d m with neuropathic arthropathy
47816	Type II diabetes mellitus with neuropathic arthropathy
66965	Type 2 diabetes mellitus with neuropathic arthropathy
18278	Insulin treated Type 2 diabetes mellitus
37648	Insulin treated non-insulin dependent diabetes mellitus
18264	Insulin treated Type II diabetes mellitus
36633	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
52236	Malnutrition-related diabetes mellitus
66675	Malnutrition-related diabetes mellitus with coma
33969	Malnutrition-related diabetes mellitus with ketoacidosis
100347	Malnutritn-relat diabetes melitus wth periph circul complctn
11551	Diabetes mellitus induced by steroids
26108	Steroid induced diabetes mellitus without complication

43453	Diabetes mellitus autosomal dominant
36695	Diabetes mellitus autosomal dominant type 2
59991	Insulin dependent diabetes mellitus
1549	Insulin-dependent diabetes mellitus with renal complications
12455	Insulin-dependent diabetes mellitus with ophthalmic comps
51261	Insulin dependent diabetes mellitus with multiple complicat
102946	Unstable insulin dependent diabetes mellitus
98071	Insulin dependent diabetes mellitus with ulcer
45276	Insulin dependent diabetes mellitus with gangrene
54600	Insulin dependent diabetes mellitus with retinopathy
98704	Insulin dependent diabetes mellitus - poor control
109051	Insulin dependent diabetes maturity onset
97849	Insulin-dependent diabetes without complication

99719	Type I diabetes mellitus with polyneuropathy
Medcode	**Read Term**
68105	Insulin dependent diabetes mellitus with polyneuropathy
91943	Insulin dependent diabetes mellitus with nephropathy
10418	Insulin dependent diabetes mellitus with hypoglycaemic coma
39070	Insulin dependent diabetes mellitus with diabetic cataract
97894	Latent autoimmune diabetes mellitus in adult
55239	Type 2 diabetes mellitus
108724	Type II diabetes mellitus
95636	Type 2 diabetes mellitus with renal complications
758	Type II diabetes mellitus with renal complications
22884	Type 2 diabetes mellitus with ophthalmic complications

18777	Type II diabetes mellitus with ophthalmic complications
57278	Type 2 diabetes mellitus with neurological complications
47321	Type II diabetes mellitus with neurological complications
100964	Type 2 diabetes mellitus with multiple complications
34268	Type II diabetes mellitus with multiple complications
98616	Type 2 diabetes mellitus with ulcer
65267	Type II diabetes mellitus with ulcer
43227	Type 2 diabetes mellitus with gangrene
49074	Type II diabetes mellitus with gangrene
91646	Type 2 diabetes mellitus with retinopathy
12736	Type II diabetes mellitus with retinopathy
104323	Type 2 diabetes mellitus - poor control
18496	Type II diabetes mellitus - poor control
49655	Reaven's syndrome
25627	Metabolic syndrome X
47315	Type 2 diabetes mellitus without complication

54773	Type II diabetes mellitus without complication
39481	Type 2 diabetes mellitus with mononeuropathy
47954	Type II diabetes mellitus with mononeuropathy
53392	Type 2 diabetes mellitus with polyneuropathy
62674	Type II diabetes mellitus with polyneuropathy
95351	Type 2 diabetes mellitus with nephropathy
18425	Type II diabetes mellitus with nephropathy
50527	Type 2 diabetes mellitus with hypoglycaemic coma
12640	Type II diabetes mellitus with hypoglycaemic coma
102201	Type 2 diabetes mellitus with diabetic cataract
46917	Type II diabetes mellitus with diabetic cataract
98723	Type 2 diabetes mellitus with peripheral angiopathy
Medcode	**Read Term**

44982	Type II diabetes mellitus with peripheral angiopathy
93727	Type 2 diabetes mellitus with arthropathy
37806	Type II diabetes mellitus with arthropathy
104639	Type 2 diabetes mellitus with neuropathic arthropathy
59253	Type II diabetes mellitus with neuropathic arthropathy
103902	Insulin treated Type 2 diabetes mellitus
35385	Insulin treated Type II diabetes mellitus
109197	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
1407	Hyperosmolar non-ketotic state in type II diabetes mellitus
64668	Type 2 diabetes mellitus with persistent proteinuria
34450	Type II diabetes mellitus with persistent proteinuria
107701	Type 2 diabetes mellitus with persistent microalbuminuria
26054	Type II diabetes mellitus with persistent microalbuminuria
60796	Type 2 diabetes mellitus with ketoacidosis

18390	Type II diabetes mellitus with ketoacidosis
85991	Type 2 diabetes mellitus with ketoacidotic coma
32627	Type II diabetes mellitus with ketoacidotic coma
106528	Type 2 diabetes mellitus with exudative maculopathy
51756	Type II diabetes mellitus with exudative maculopathy
106061	Type 2 diabetes mellitus with gastroparesis
25591	Maternally inherited diabetes mellitus
111798	Secondary pancreatic diabetes mellitus
63690	Secondary pancreatic diabetes mellitus without complication
95539	Diabetes mellitus induced by non-steroid drugs
51697	DM induced by non-steroid drugs without complication
96506	Insulin autoimmune syndrome
61122	Type A insulin resistance
67212	Type A insulin resistance without complication
68517	Lipoatrophic diabetes mellitus

37957	Secondary diabetes mellitus
56885	Secondary diabetes mellitus without complication
43857	Cystic fibrosis related diabetes mellitus
22487	Diabetes mellitus in remission
107603	Type II diabetes mellitus in remission
108360	Type 2 diabetes mellitus in remission
109628	Diabetes mellitus with other specified manifestation
Medcode	**Read Term**
107824	Diabetes mellitus, juvenile, + other specified manifestation
110611	Diabetes mellitus, adult, + other specified manifestation
33343	Other specified diabetes mellitus with other spec comps
110997	Diabetes mellitus NOS with other specified manifestation
63371	Diabetes mellitus with unspecified complication
10098	Diabetes mellitus, juvenile type, + unspecified complication

70821	Diabetes mellitus, adult onset, + unspecified complication
45491	Other specified diabetes mellitus with unspecified comps
68792	Diabetes mellitus NOS with unspecified complication
711	**Diabetes mellitus**
3550	Diabetic monitoring
14889	Maturity onset diabetes
28873	Diabetic 6 month review
83532	Diabetes type 2 review
101801	Type II diabetic dietary review
101177	Diabetic dietary review
Jaw pain	
1286	[D]Jaw pain
24905	Difficulty chewing

Table 2: Prodcode list for corticosteroids used to define GCA population in sensitivity analysis.

Prodcode	**Product name**
44	Prednisolone 5mg gastro-resistant tablets
95	Prednisolone 5mg tablets
186	Dexamethasone 500micrograms/5ml oral solution
229	Cortisone 25mg tablets
557	Prednisolone 2.5mg gastro-resistant tablets
578	Prednisolone 1mg tablets
955	Prednisolone 5mg soluble tablets
1063	Prednisolone sodium phosphate
1280	Dexamethasone 2mg tablets
1709	
1971	Betnesol 500microgram soluble tablets (Focus Pharmaceuticals Ltd)
2044	PREDNISONE 2.5 MG TAB
2130	Methylprednisolone 4mg tablets
2368	Prednisolone 2.5mg tablet
2390	PREDNISOLONE E/C 1 MG TAB
2704	Prednisolone 25mg tablets
2799	PREDNISOLONE 10 MG TAB
2949	Prednisone 5mg tablets

3059	PREDNISOLONE 50 MG TAB
3345	Sintisone Tablet (Pharmacia Ltd)
3418	Hydrocortisone 10mg tablets
3543	CHLORAMPHENICOL&HYDROCORTISONE oint EYE
3557	Prednisone 1mg tablets
3969	DEXAMETHASONE 8 MG TAB
3992	Deflazacort 6mg tablets
4535	Hydrocortisone 20mg tablets
4779	Dexamethasone 500microgram tablets
4943	Dexamethasone 2mg/5ml oral solution sugar free
5157	Dexamethasone 2mg/5ml oral solution
5490	Deltacortril 5mg gastro-resistant tablets (Alliance Pharmaceuticals Ltd)
5913	Deltacortril 2.5mg gastro-resistant tablets (Alliance Pharmaceuticals Ltd)
6098	Hydrocortone 10mg tablets (Auden McKenzie (Pharma Division) Ltd)
7286	Betamethasone 500microgram soluble tablets sugar free
7548	Cortisone 5mg capsules
7584	PREDNISOLONE 4 MG TAB

7710	PREDNISOLONE 15 MG TAB
7934	PREDNISONE 30 MG TAB
8261	Medrone 16mg tablets (Pfizer Ltd)
9375	Deflazacort 1mg tablets
9727	Prednisolone 50mg tablets
9994	Decadron 500microgram tablets (Merck Sharp & Dohme Ltd)
10552	Methylprednisolone 16mg tablets
10574	Cortisone acetate 5mg tablets
10683	Medrone 2mg tablets (Pfizer Ltd)
10684	Methylprednisolone 2mg tablets
10754	Hydrocortistab 20mg Tablet (Waymade Healthcare Plc)
10864	Betamethasone 500microgram tablets
11149	Betnelan 500microgram tablets (Focus Pharmaceuticals Ltd)
12398	Cortelan 25mg Tablet (Glaxo Laboratories Ltd)
12400	Cortisyl 25mg Tablet (Aventis Pharma)
13043	Hydrocortone 20mg tablets (Auden McKenzie (Pharma Division) Ltd)
13522	PREDNISOLONE 2 MG TAB
13615	PREDNISONE 10 MG TAB

14076	Hydrocortisone 5mg/5ml Oral solution
14172	Methylprednisolone 100mg tablets
15471	HYDROCORTISONE 25 MG TAB
15555	Medrone 4mg tablets (Pfizer Ltd)
15617	Ledercort 4mg Tablet (Wyeth Pharmaceuticals)
16724	PREDNISONE 50 MG TAB
17101	DEXAMETHASONE 750 MCG TAB
17410	Deflazacort 30mg tablets
18042	Medrone 100mg tablets (Pfizer Ltd)
18637	Cortistab 25mg Tablet (Waymade Healthcare Plc)
19141	Prednisolone 5mg soluble tablets (AMCo)
19908	Triamcinolone 2mg Tablet
20095	Precortisyl forte 25mg Tablet (Aventis Pharma)
20577	Calcort 6mg Tablet (Shire Pharmaceuticals Ltd)
20670	PREDNISOLONE E/C
21218	Dexsol 2mg/5ml oral solution (Rosemont Pharmaceuticals Ltd)
21417	Prednisolone 5mg tablets (A A H Pharmaceuticals Ltd)

21465	BETAMETHASONE .1 MG TAB
21833	Decortisyl 5mg Tablet (Roussel Laboratories Ltd)
21903	Oradexon-organon 2mg Tablet (Organon Laboratories Ltd)
22555	Calcort 1mg tablets (Shire Pharmaceuticals Ltd)
22827	BETAMETHASONE .1 MG PEL
22894	HYDROCORTISONE 4 MG PAS
23111	Triamcinolone 4mg Tablet
23210	Cortistab 5mg Tablet (Waymade Healthcare Plc)
23512	Precortisyl 5mg Tablet (Hoechst Marion Roussel)
24014	Ledercort 2mg Tablet (Wyeth Pharmaceuticals)
24716	PREDNISOLONE E/C
25272	Precortisyl 1mg Tablet (Hoechst Marion Roussel)
27083	BETAMETHASONE VALERATE .1 MG TAB
27889	PREDNISOLONE
27959	PREDNISOLONE

27962	Deltastab 1mg Tablet (Waymade Healthcare Plc)
28375	Prednisolone 2.5mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)
28376	Prednisolone 2.5mg Gastro-resistant tablet (Biorex Laboratories Ltd)
28859	Deltastab 5mg Tablet (Waymade Healthcare Plc)
29112	Calcort 30mg tablets (Shire Pharmaceuticals Ltd)
29333	Prednisolone 5mg tablets (Actavis UK Ltd)
31327	Prednisolone steaglate 6.65mg tablet
31532	Prednisolone 5mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)
32803	Prednisolone 5mg gastro-resistant tablets (Actavis UK Ltd)
32835	Prednisolone 5mg tablets (Wockhardt UK Ltd)
33691	Prednisolone 5mg Gastro-resistant tablet (Biorex Laboratories Ltd)
33988	Prednisolone 5mg Tablet (Co-Pharma Ltd)
33990	Prednisolone 5mg Tablet (IVAX Pharmaceuticals UK Ltd)

34109	Prednisolone 5 mg gastro-resistant tablet
34393	Prednisolone 5mg gastro-resistant tablets (Teva UK Ltd)
34404	Prednisolone 1mg tablets (Actavis UK Ltd)
34452	Prednisolone 1mg tablets (A A H Pharmaceuticals Ltd)
34461	Prednisolone 2.5mg gastro-resistant tablets (Actavis UK Ltd)
34631	Prednisolone 1mg Tablet (Co-Pharma Ltd)
34660	Prednisolone 1mg tablets (Kent Pharmaceuticals Ltd)
34748	Prednisolone 1mg tablets (Teva UK Ltd)
34781	Prednisolone 5mg tablets (Kent Pharmaceuticals Ltd)
34801	Dexamethasone 0.5mg/5ml Oral solution (Rosemont Pharmaceuticals Ltd)
34880	Dexamethasone 2mg tablets (Aspen Pharma Trading Ltd)
34914	Prednisolone 1mg Tablet (Celltech Pharma Europe Ltd)
34915	Dexamethasone 500microgram tablets (Organon Laboratories Ltd)

34978	Prednisolone 1mg tablets (Wockhardt UK Ltd)
36055	Dexamethasone 2mg Tablet (Hillcross Pharmaceuticals Ltd)
38022	Hydrocortisone 10mg/5ml oral suspension
38054	Hydrocortisone Tablet
38407	Prednisolone 20mg tablet
41335	Calcort 6mg tablets (Sanofi)
41515	Prednisolone 5mg tablets (Teva UK Ltd)
41745	Prednisolone 25mg tablets (Zentiva)
43544	Prednisone 5mg Tablet (Knoll Ltd)
44380	Prednisone 1mg modified-release tablets
44723	Prednisone 5mg modified-release tablets
44802	Lodotra 5mg modified-release tablets (Napp Pharmaceuticals Ltd)
44803	Lodotra 2mg modified-release tablets (Napp Pharmaceuticals Ltd)
45234	Dexamethasone 100microgram capsules
45302	Prednisolone 5mg Tablet (Biorex Laboratories Ltd)
46711	Prednisone 2mg modified-release tablets
47142	Prednisolone 5mg Soluble tablet (Amdipharm Plc)

50225	Betnesol 500microgram soluble tablets (Waymade Healthcare Plc)
51722	Hydrocortisone 5mg/5ml oral suspension
51753	Prednisolone 1mg tablets (Strides Shasun (UK) Ltd)
51824	Hydrocortisone 5mg/5ml oral suspension sugar free
51849	Hydrocortisone 1mg/5ml oral suspension
51871	Hydrocortisone 2mg capsules
51872	Hydrocortisone 2.5mg capsules
52053	Hydrocortisone 3mg/5ml oral suspension
52396	Dexamethasone 1mg/5ml oral solution
53143	Cortisone 25mg tablets (A A H Pharmaceuticals Ltd)
53207	Dexamethasone tablets
53313	Prednisolone 20mg/5ml oral suspension
53336	Prednisolone 25mg tablets (A A H Pharmaceuticals Ltd)
53705	Cortisone acetate 5mg Capsule (Martindale Pharmaceuticals Ltd)
54118	Prednisolone 25mg/5ml oral suspension
54432	Lodotra 1mg modified-release tablets (Napp Pharmaceuticals Ltd)

54434	Prednisolone 2.5mg/5ml oral suspension
54793	Dexamethasone 2mg/5ml oral suspension
54794	Hydrocortisone 20mg modified-release tablets
55024	Prednisolone 5mg/5ml oral solution
55401	Dexamethasone 500microgram tablets (A A H Pharmaceuticals Ltd)
55480	Prednisolone 2.5mg gastro-resistant tablets (Alliance Pharmaceuticals Ltd)
56347	Dexamethasone 5mg/5ml oral solution
56443	Dexamethasone 10mg/5ml oral solution
56891	Prednisolone 1mg tablets (Waymade Healthcare Plc)
57931	Hydrocortisone 20mg tablets (Teva UK Ltd)
58000	Prednisolone 5mg tablets (Almus Pharmaceuticals Ltd)
58234	Prednisolone 10mg/5ml oral solution
58369	Prednisolone 5mg tablets (Boston Healthcare Ltd)
58384	Prednisolone 1mg tablets (Almus Pharmaceuticals Ltd)
58987	Prednisolone 5mg gastro-resistant tablets (Phoenix Healthcare Distribution Ltd)

59229	Dilacort 5mg gastro-resistant tablets (Auden McKenzie (Pharma Division) Ltd)
59283	Dilacort 2.5mg gastro-resistant tablets (Auden McKenzie (Pharma Division) Ltd)
59338	Prednisolone 1mg/5ml oral solution
59912	Prednisolone 5mg gastro-resistant tablets (Waymade Healthcare Plc)
60120	Dexamethasone 2mg tablets (Alliance Healthcare (Distribution) Ltd)
60421	Prednisolone 5mg tablets (Strides Shasun (UK) Ltd)
61132	Prednisolone 1mg tablets (Boston Healthcare Ltd)
61162	Prednisolone 5mg tablets (Waymade Healthcare Plc)
62909	Dexamethasone 2mg tablets (A A H Pharmaceuticals Ltd)
63066	Prednisolone 2.5mg tablets
63549	Prednisolone 1mg/ml oral solution (Logixx Pharma Solutions Ltd)
64007	Pevanti 10mg tablets (AMCo)
64008	Pevanti 2.5mg tablets (AMCo)
64059	Hydrocortisone 2.5mg/5ml oral suspension

64128	Pevanti 5mg tablets (AMCo)
64221	Prednisolone 5mg/5ml oral suspension
64787	Hydrocortisone 10mg tablets (Almus Pharmaceuticals Ltd)
65626	Prednisolone 10mg/5ml oral suspension
65984	Hydrocortisone 10mg tablets (Actavis UK Ltd)
66327	Hydrocortisone 20mg tablets (Actavis UK Ltd)
66550	Prednisolone 5mg gastro-resistant tablets (Alliance Healthcare (Distribution) Ltd)
66666	Hydrocortisone 10mg tablets (Teva UK Ltd)
67107	Prednisolone 5mg gastro-resistant tablets (Alliance Pharmaceuticals Ltd)
67559	Prednisolone 5mg/5ml oral solution unit dose (A A H Pharmaceuticals Ltd)
68182	Dexamethasone 2mg tablets (Teva UK Ltd)
68489	Dexamethasone 4mg tablets
68497	Prednisolone 2.5mg gastro-resistant tablets (Waymade Healthcare Plc)
68593	Dexamethasone 5mg/5ml oral suspension
69568	Dilacort 5mg gastro-resistant tablets (Crescent Pharma Ltd)

69572	Dexamethasone 4mg/5ml oral suspension
69686	Pevanti 25mg tablets (AMCo)

Appendix 5.1 – Results tables for Incidence/prevalence

Table 1: Annual consultation incidence per 10,000 person-years (P-Y) for 1990-2017, with 95% confidence intervals. The consultation incidence for 1990 cannot be reported here as there were less than 5 incidence cases.

Year	GCA cases	Incidence per 10,000 P-Y	95% CI
1990	-	-	-
1991	36	0.76	(0.55, 1.05)
1992	104	1.88	(1.55, 2.28)
1993	137	2.14	(1.81, 2.53)
1994	161	2.29	(1.96, 2.67)
1995	172	2.24	(1.93, 2.60)
1996	175	1.97	(1.70, 2.28)
1997	172	1.63	(1.40, 1.89)
1998	224	1.85	(1.63, 2.11)
1999	227	1.56	(1.37, 1.77)
2000	251	1.42	(1.26, 1.61)
2001	279	1.40	(1.24, 1.57)
2002	404	1.76	(1.60, 1.94)
2003	398	1.59	(1.44, 1.75)
2004	475	1.74	(1.59, 1.91)
2005	497	1.74	(1.59, 1.90)
2006	448	1.51	(1.38, 1.66)

2007	524	1.72	(1.58, 1.87)
2008	491	1.57	(1.44, 1.72)
2009	545	1.71	(1.57, 1.86)
2010	492	1.53	(1.40, 1.67)
2011	549	1.71	(1.57, 1.86)
2012	483	1.49	(1.36, 1.63)
2013	484	1.52	(1.39, 1.67)
2014	431	1.44	(1.31, 1.58)
2015	441	1.66	(1.51, 1.82)
2016	314	1.43	(1.28, 1.59)
2017	279	1.46	(1.30, 1.64)

Table 2: Annual consultation incidence rates of GCA in the UK from the sensitivity analysis using glucocorticoids to define GCA. Results from 8244 GCA cases. The consultation incidence for 1990 cannot be reported here as there were less than 5 incidence cases.

Year	**Incidence per 10,000 P-Y**	**95% CI**
1990	-	-
1991	0.65	(0.46, 0.93)
1992	1.62	(1.32, 2.00)
1993	1.90	(1.59, 2.27)
1994	1.95	(1.65, 2.30)
1995	2.01	(1.71, 2.35)
1996	1.74	(1.49, 2.04)
1997	1.46	(1.25, 1.71)
1998	1.58	(1.37, 1.82)
1999	1.38	(1.20, 1.58)
2000	1.26	(1.10, 1.44)
2001	1.23	(1.08, 1.39)
2002	1.48	(1.33, 1.64)
2003	1.40	(1.26, 1.55)
2004	1.53	(1.39, 1.69)
2005	1.55	(1.41, 1.70)
2006	1.35	(1.23, 1.49)
2007	1.55	(1.42, 1.70)
2008	1.44	(1.32, 1.58)

2009	1.56	(1.43, 1.70)
2010	1.41	(1.29, 1.55)
2011	1.57	(1.44, 1.71)
2012	1.36	(1.24, 1.50)
2013	1.39	(1.27, 1.53)
2014	1.30	(1.18, 1.44)
2015	1.51	(1.36, 1.66)
2016	1.29	(1.15, 1.45)
2017	1.29	(1.14, 1.46)

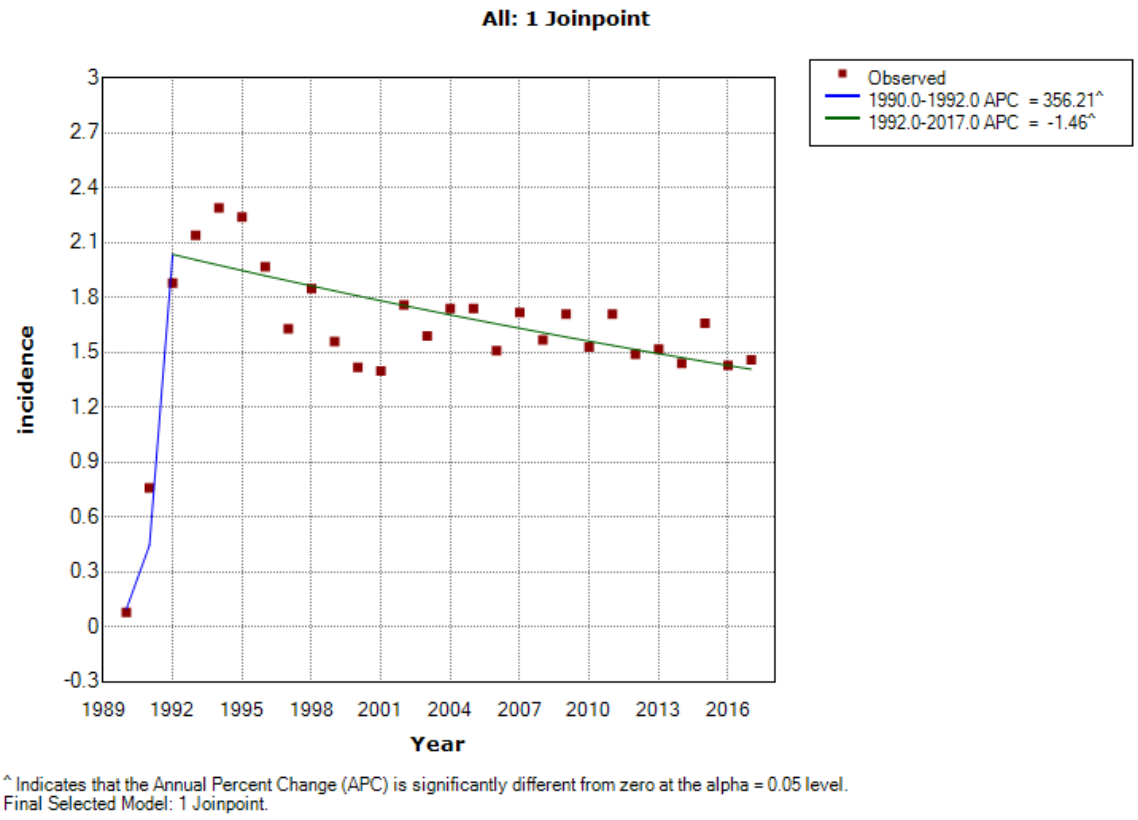

Figure 1: Joinpoint regression model for annual consultation incidence of GCA for Monte Carlo permutation test model selection using all time points.

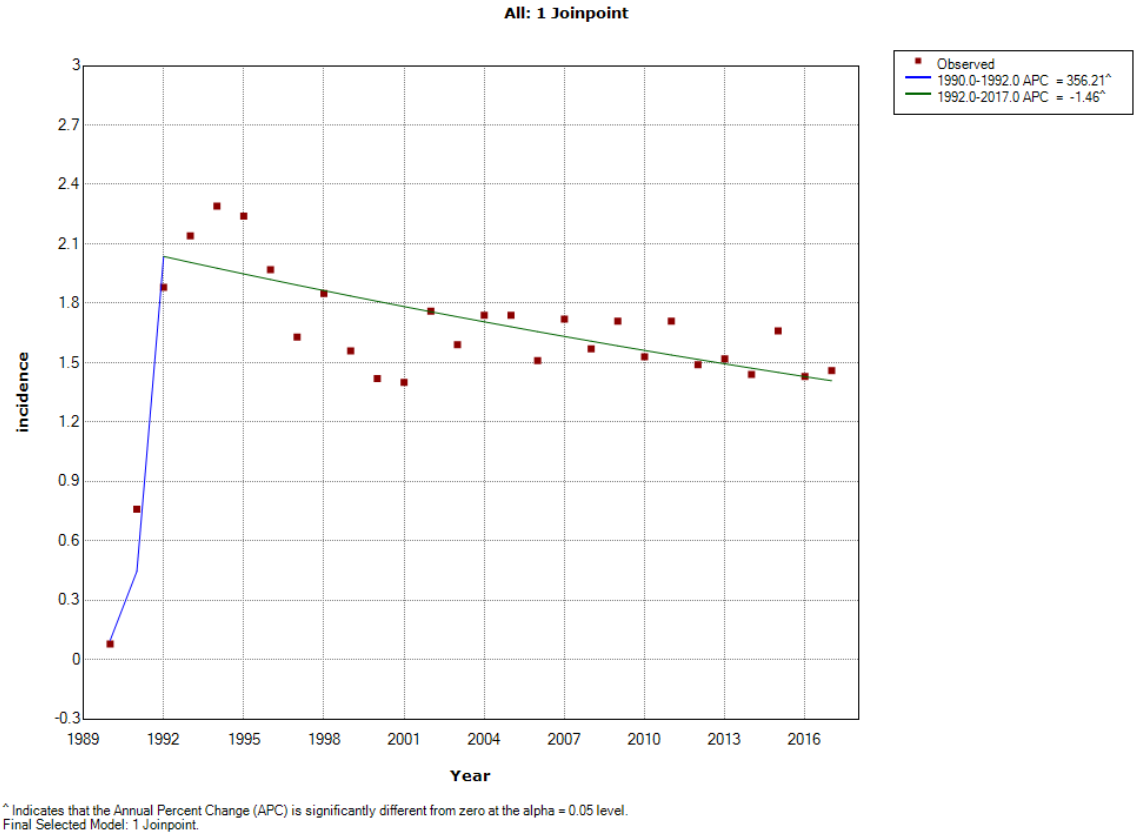

Figure 2: Joinpoint model for annual consultation incidence of GCA for modified BIC model selection using all time points.

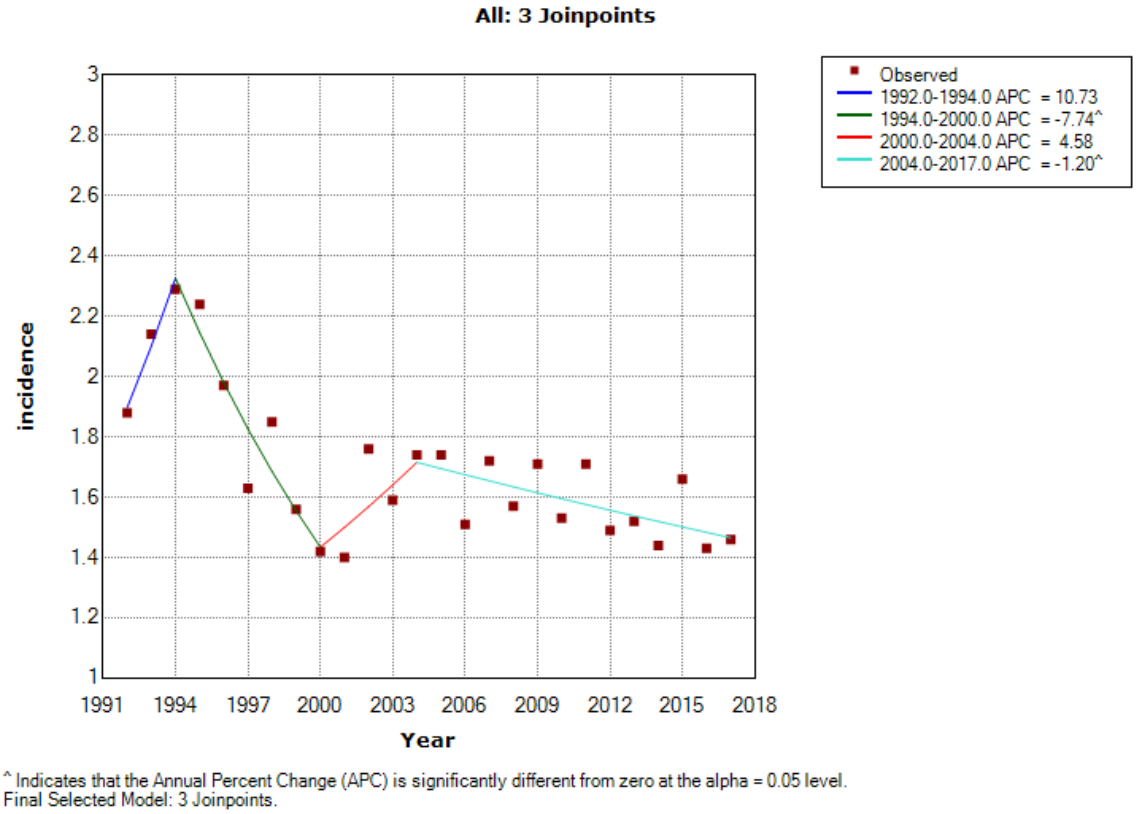

Figure 3: Joinpoint model for annual consultation incidence of GCA showing the Monte Carlo permutation test selection.

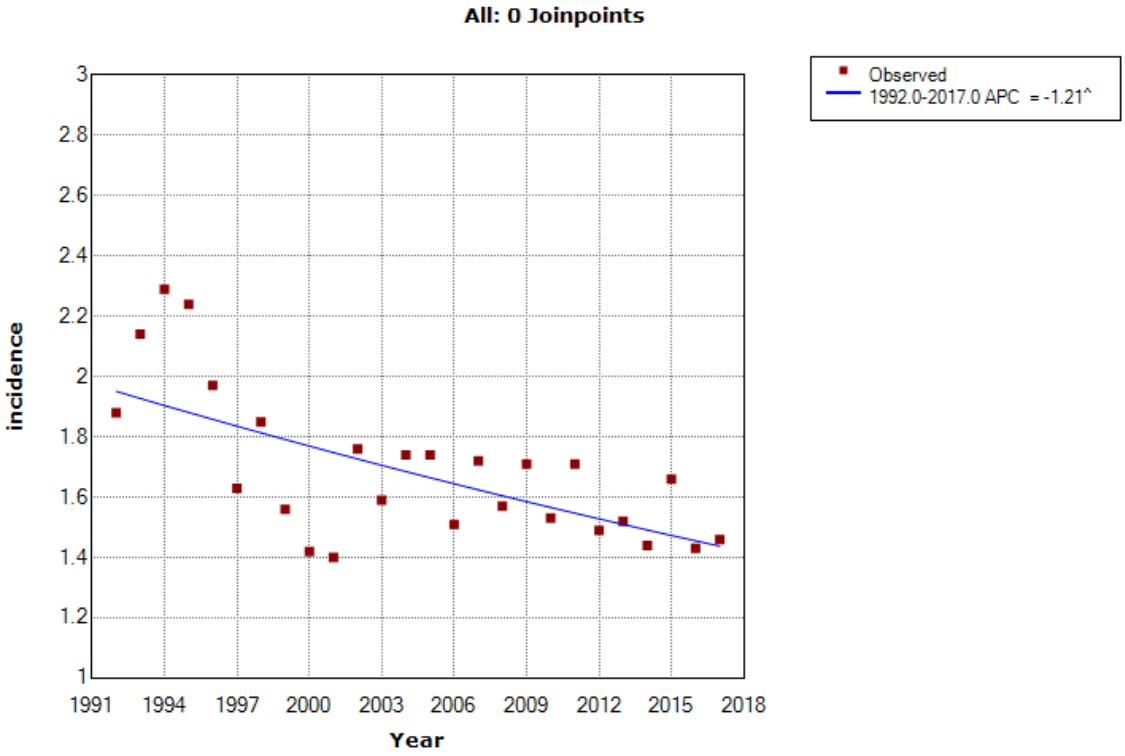

Figure 4: Joinpoint model for annual consultation incidence of GCA showing the modified BIC selection.

Table 3: Annual consultation incidence of GCA per 10,000 P-Y stratified by gender.

Year	Gender	GCA cases	Consultation Incidence per 10,000 P-Y	Lower 95% CI	Upper 95% CI
1990	male	1	0.06	0.01	0.42
	female	2	0.10	0.03	0.42
1991	male	13	0.58	0.34	1.00
	female	23	0.91	0.61	1.40
1992	male	33	1.30	0.90	1.80
	female	71	2.40	1.90	3.00
1993	male	30	1.00	0.70	1.40
	female	107	3.10	2.60	3.80
1994	male	51	1.50	1.20	2.00
	female	110	2.90	2.40	3.50
1995	male	66	1.80	1.40	2.30
	female	106	2.60	2.20	3.10
1996	male	55	1.30	1.00	1.70
	female	120	2.50	2.10	3.00
1997	male	47	0.95	0.71	1.30
	female	125	2.20	1.90	2.70
1998	male	55	0.96	0.74	1.30
	female	169	2.60	2.30	3.10
1999	male	63	0.91	0.71	1.20

	female	164	2.10	1.80	2.50
2000	male	72	0.86	0.69	1.10
	female	179	1.90	1.70	2.20
2001	male	68	0.72	0.57	0.91
	female	211	2.00	1.80	2.30
2002	male	114	1.00	0.87	1.30
	female	290	2.40	2.10	2.70
2003	male	116	0.97	0.81	1.20
	female	282	2.10	1.90	2.40
2004	male	145	1.10	0.95	1.30
	female	330	2.30	2.10	2.60
2005	male	134	0.99	0.83	1.20
	female	363	2.40	2.20	2.70
2006	male	129	0.92	0.77	1.10
	female	319	2.10	1.80	2.30
2007	male	152	1.00	0.89	1.20
	female	372	2.30	2.10	2.60
2008	male	127	0.86	0.72	1.00
	female	364	2.20	2.00	2.50
2009	male	168	1.10	0.95	1.30
	female	377	2.30	2.00	2.50
2010	male	142	0.93	0.79	1.10

	female	350	2.10	1.90	2.30
2011	male	168	1.10	0.95	1.30
	female	381	2.30	2.00	2.50
2012	male	143	0.93	0.79	1.10
	female	340	2.00	1.80	2.20
2013	male	140	0.93	0.79	1.10
	female	344	2.10	1.90	2.30
2014	male	131	0.92	0.78	1.10
	female	300	1.90	1.70	2.10
2015	male	133	1.10	0.89	1.20
	female	308	2.20	2.00	2.50
2016	male	97	0.93	0.76	1.10
	female	217	1.90	1.60	2.20
2017	male	78	0.85	0.68	1.10
	female	201	2.00	1.80	2.30

Table 4: Consultation incidence of GCA per 10,000 P-Y stratified by age and gender.

Age (years)	Gender	GCA cases	Consultation Incidence per 10,000 P-Y	95% CI
40-49	male	63	0.08	(0.06, 0.10)
	female	181	0.22	(0.19, 0.26)
50-59	male	261	0.37	(0.33, 0.41)
	female	639	0.91	(0.84, 0.98)
60-69	male	685	1.20	(1.10, 1.30)
	female	1539	2.60	(2.50, 2.70)
70-79	male	1055	2.70	(2.60, 2.90)
	female	2463	5.20	(5.00, 5.40)
80-89	male	562	3.10	(2.80, 3.40)
	female	1516	5.00	(4.70, 5.20)
90+	male	45	1.10	(0.85, 1.50)
	female	187	1.90	(1.70, 2.20)

Table 5: Annual consultation prevalence of GCA results from 1990-2017 showing prevalence per 10,000 person-years with 95% confidence intervals.

Year	Cons. Prevalence per 10,000 P-Y	95% CI
1990	0.025	(0.005, 0.074)
1991	0.289	(0.202, 0.400)
1992	0.852	(0.702, 1.025)
1993	1.184	(1.010, 1.380)
1994	1.491	(1.299, 1.703)
1995	1.494	(1.306, 1.701)
1996	1.512	(1.328, 1.715)
1997	1.459	(1.282, 1.654)
1998	1.739	(1.549, 1.945)
1999	1.683	(1.501, 1.881)
2000	1.903	(1.713, 2.108)
2001	2.023	(1.831, 2.229)
2002	2.539	(2.328, 2.763)
2003	2.658	(2.447, 2.882)
2004	2.895	(2.679, 3.123)
2005	2.941	(2.728, 3.167)
2006	2.596	(2.399, 2.804)

2007	2.749	(2.550, 2.958)
2008	2.562	(2.374, 2.761)
2009	2.760	(2.568, 2.963)
2010	2.541	(2.360, 2.733)
2011	2.558	(2.379, 2.747)
2012	2.302	(2.135, 2.479)
2013	2.152	(1.993, 2.321)
2014	1.909	(1.761, 2.066)
2015	1.792	(1.650, 1.942)
2016	1.287	(1.169, 1.414)
2017	1.105	(0.997, 1.221)

Table 6: Crude consultation prevalence and age-adjusted consultation prevalence of GCA per 10,000 P-Y with 95% confidence intervals.

Year	GCA consultations	Crude consultation prevalence per 10,000 P-Y	95% CI	Age-adjusted consultation prevalence per 10,000 P-Y	95% CI
1990	5	0.121	(0.039, 0.283)	0.125	(0.040, 0.322)
1991	52	1.021	(0.763, 1.339)	1.030	(0.769, 1.366)
1992	206	3.518	(3.054, 4.033)	3.463	(3.005, 3.980)
1993	357	5.601	(5.035, 6.213)	5.535	(4.974, 6.148)
1994	438	6.301	(5.725, 6.920)	6.276	(5.701, 6.900)
1995	508	6.860	(6.276, 7.483)	6.825	(6.243, 7.452)
1996	475	5.375	(4.903, 5.881)	5.365	(4.893, 5.875)
1997	505	4.936	(4.515, 5.386)	4.943	(4.520, 5.397)
1998	600	4.939	(4.552, 5.351)	4.982	(4.590, 5.399)
1999	673	4.461	(4.130, 4.811)	4.536	(4.199, 4.894)

2000	814	4.681	(4.365, 5.014)	4.769	(4.446, 5.109)
2001	931	4.661	(4.367, 4.970)	4.797	(4.494, 5.117)
2002	1216	5.502	(5.197, 5.820)	5.705	(5.388, 6.036)
2003	1274	5.283	(4.997, 5.581)	5.521	(5.222, 5.833)
2004	1411	5.559	(5.273, 5.857)	5.843	(5.542, 6.157)
2005	1444	5.537	(5.255, 5.830)	5.858	(5.559, 6.168)
2006	1348	5.105	(4.836, 5.385)	5.388	(5.104, 5.684)
2007	1421	5.342	(5.068, 5.627)	5.609	(5.321, 5.909)
2008	1478	5.535	(5.256, 5.824)	5.792	(5.500, 6.095)
2009	1604	6.003	(5.713, 6.304)	6.275	(5.972, 6.591)
2010	1517	5.781	(5.493, 6.079)	6.053	(5.752, 6.366)
2011	1499	5.820	(5.529, 6.122)	6.092	(5.787, 6.409)
2012	1314	5.172	(4.896, 5.459)	5.414	(5.125, 5.715)
2013	1273	5.328	(5.039, 5.628)	5.539	(5.238, 5.852)

2014	1178	5.521	(5.211, 5.846)	5.696	(5.375, 6.031)
2015	1041	6.037	(5.676, 6.415)	6.186	(5.816, 6.574)
2016	756	5.213	(4.848, 5.598)	5.391	(5.013, 5.790)
2017	652	5.035	(4.656, 5.437)	5.131	(4.744, 5.541)

Table 7: Incidence rates of GCA stratified by age for the 8244 sensitivity GCA cases.

Age (years)	**Incidence per 10,000 P-Y**	**95% CI**
40-49	0.10	(0.09, 0.12)
50-59	0.53	(0.49, 0.57)
60-69	1.70	(1.70, 1.80)
70-79	3.80	(3.60, 3.90)
80-89	3.90	(3.70, 4.10)
90+	1.40	(1.20, 1.60)

Table 8: Incidence rates of GCA stratified by age and gender including the 8244 GCA cases in the sensitivity analysis.

Age (years)	Gender	Incidence per 10,000 P-Y	95% CI
40-49	male	0.05	(0.03, 0.06)
40-40	female	0.15	(0.13, 0.18)
50-59	male	0.30	(0.26, 0.34)
50-59	female	0.75	(0.69, 0.82)
60-69	male	1.00	(0.95, 1.10)
60-69	female	2.40	(2.30, 2.50)
70-79	male	2.50	(2.40, 2.70)
70-79	female	4.80	(4.60, 5.00)
80-89	male	2.90	(2.60, 3.10)
80-89	female	4.60	(4.30, 4.80)
90+	male	0.91	(0.66, 1.30)
90+	female	1.60	(1.40, 1.90)

Table 9: Annual incidence rates of GCA stratified by gender for the 8244 GCA cases from the sensitivity analysis.

Year	Gender	Incidence per 10,000 P-Y	95% CI
1990	male	0.06	(0.01, 0.42)
1990	female	0.05	(0.01, 0.37)
1991	male	0.49	(0.27, 0.89)
1991	female	0.79	(0.51, 1.20)
1992	male	1.10	(0.74, 1.60)
1992	female	2.10	(1.60, 2.70)
1993	male	0.86	(0.59, 1.30)
1993	female	2.80	(2.30, 3.40)
1994	male	1.20	(0.91, 1.70)
1994	female	2.60	(2.10, 3.10)
1995	male	1.50	(1.10, 2.00)
1995	female	2.50	(2.00, 3.00)
1996	male	1.10	(0.85, 1.50)
1996	female	2.30	(1.90, 2.80)
1997	male	0.83	(0.61, 1.10)
1997	female	2.00	(1.70, 2.40)
1998	male	0.84	(0.63, 1.10)
1998	female	2.20	(1.90, 2.60)
1999	male	0.81	(0.62, 1.10)
1999	female	1.90	(1.60, 2.20)

2000	male	0.77	(0.60, 0.98)
2000	female	1.70	(1.50, 2.00)
2001	male	0.63	(0.49, 0.82)
2001	female	1.80	(1.50, 2.00)
2002	male	0.84	(0.68, 1.00)
2002	female	2.10	(1.80, 2.30)
2003	male	0.85	(0.70, 1.00)
2003	female	1.90	(1.70, 2.10)
2004	male	0.96	(0.80, 1.10)
2004	female	2.10	(1.80, 2.30)
2005	male	0.88	(0.73, 1.00)
2005	female	2.20	(1.90, 2.40)
2006	male	0.80	(0.67, 0.96)
2006	female	1.90	(1.70, 2.10)
2007	male	0.95	(0.80, 1.10)
2007	female	2.10	(1.90, 2.30)
2008	male	0.75	(0.63, 0.91)
2008	female	2.10	(1.90, 2.30)
2009	male	1.00	(0.87, 1.20)
2009	female	2.00	(1.80, 2.30)
2010	male	0.82	(0.69, 0.98)
2010	female	1.90	(1.70, 2.20)
2011	male	0.99	(0.84, 1.20)

2011	female	2.10	(1.90, 2.30)
2012	male	0.84	(0.71, 1.00)
2012	female	1.80	(1.60, 2.10)
2013	male	0.85	(0.71, 1.00)
2013	female	1.90	(1.70, 2.10)
2014	male	0.83	(0.69, 1.00)
2014	female	1.70	(1.50, 1.90)
2015	male	0.98	(0.82, 1.20)
2015	female	2.00	(1.80, 2.20)
2016	male	0.85	(0.69, 1.00)
2016	female	1.70	(1.50, 1.90)
2017	male	0.72	(0.57, 0.92)
2017	female	1.80	(1.60, 2.10)

Table 10: Incidence rate per 10,000 P-Y of GCA in the UK, stratified by region and year for the sensitivity analysis with 8244 GCA cases

Region	**1990-1994**		**1995-1999**		**2000-2004**		**2005-2009**		**2010-2014**		**2015-2017**	
	Incidence	95% CI	Incidence	95% CI	Incidence	95% CI	Incidence	95% CI	Incidence	95% CI	Incidence	95% CI
North East	2.32	(1.32, 4.09)	1.34	(0.82, 2.18)	1.23	(0.82, 1.85)	1.79	(1.32, 2.43)	1.14	(0.77, 1.68)	1.13	(0.51, 2.51)
North West	1.79	(1.38, 2.32)	1.89	(1.58, 2.26)	1.62	(1.41, 1.86)	1.41	(1.23, 1.61)	1.63	(1.44, 1.85)	1.10	(0.81, 1.48)
Yorkshire & the Humber	2.48	(1.89, 3.27)	2.30	(1.83, 2.88)	1.71	(1.38, 2.12)	1.64	(1.32, 2.04)	1.31	(0.91, 1.89)	2.63	(1.49, 4.63)
East Midlands	2.10	(1.54, 2.86)	1.83	(1.42, 2.36)	2.11	(1.75, 2.56)	1.92	(1.57, 2.34)	1.82	(1.29, 2.57)	-	-
West Midlands	0.96	(0.63, 1.48)	1.45	(1.15, 1.81)	1.60	(1.38, 1.87)	1.46	(1.26, 1.69)	1.51	(1.32, 1.74)	0.92	(0.67, 1.26)
East of England	2.13	(1.63, 2.79)	1.88	(1.53, 2.30)	1.83	(1.59, 2.11)	1.84	(1.61, 2.10)	1.56	(1.33, 1.83)	1.57	(1.16, 2.13)
South West	1.58	(1.12, 2.23)	1.93	(1.56, 2.40)	1.72	(1.48, 2.00)	1.70	(1.50, 1.93)	1.62	(1.43, 1.83)	1.92	(1.52, 2.42)
South Central	1.23	(0.82, 1.86)	1.62	(1.26, 2.07)	1.40	(1.19, 1.64)	1.45	(1.27, 1.65)	1.36	(1.21, 1.54)	1.48	(1.20, 1.82)

London	1.53	(1.05, 2.23)	1.39	(1.07, 1.82)	1.08	(0.88, 1.32)	1.17	(0.99, 1.39)	0.98	(0.83, 1.16)	1.31	(1.02, 1.67)
South East Coast	1.11	(0.72, 1.70)	2.42	(1.97, 2.96)	1.63	(1.39, 1.91)	1.67	(1.47, 1.90)	1.63	(1.45, 1.85)	1.26	(1.03, 1.53)
Northern Ireland	1.48	(0.55, 3.93)	2.83	(1.99, 4.03)	1.08	(0.78, 1.50)	1.21	(0.94, 1.56)	1.16	(0.91, 1.48)	1.71	(1.32, 2.22)
Scotland	1.16	(0.58, 2.31)	1.20	(0.82, 1.76)	0.79	(0.63, 1.00)	1.52	(1.34, 1.73)	1.58	(1.41, 1.78)	1.74	(1.52, 2.01)
Wales	1.38	(0.97, 1.96)	1.59	(1.25, 2.04)	1.42	(1.20, 1.68)	1.98	(1.77, 2.23)	1.91	(1.72, 2.13)	2.09	(1.83, 2.38)

Appendix 6.1 – Code lists and results tables for the case-control study

Table 1: Code list for alcohol consumption, smoking status, and BMI used to define the variables for the analysis.

Demographic	**Medcode**	**Read code**	**Read Term**
Alcohol Consumption	27	136..00	Alcohol consumption
	93415	136V.00	Alcohol units per week
	12980	136N.00	light drinker (1-2 u/day)
	749	1362.12	Drinks occasionally
	385	1362.11	Drinks rarely
	12985	136O.00	Moderate drinker
	12970	1361.11	Non drinker alcohol
	12979	136M.00	Current non drinker
	4447	1362.12	Non-drinker alcohol
	8999	136P.00	Heavy drinker (7-9 units/day
	12984	136Q.00	Very heavy drinker (>9 u/day)
	12985	136O.00	Moderate drinker
	27	136..00	Alcohol consumption
	93415	136V.00	Alcohol units per week
	12980	136N.00	light drinker (1-2 u/day)

	27	136..00	Alcohol consumption
	93415	136V.00	Alcohol units per week
	749	1362.12	Drinks occasionally
	385	1362.11	Drinks rarely
	8999	136P.00	Heavy drinker (7-9 units/day
	12984	136Q.00	Very heavy drinker (>9 u/day)
	27	136..00	Alcohol consumption
	93415	136V.00	Alcohol units per week
	97126	136X.00	lcohol units consumed on heaviest drinking day
	12970	1361.11	Non drinker alcohol
	12979	136M.00	Current non drinker
	4447	1362.12	Non-drinker alcohol
Smoking Status			
	12964	137C.00	Keeps trying to stop smoking
	31114	137b.00	Ready to stop smoking
	9045	ZG23300	Advice on smoking
	18926	67H1.00	Lifestyle advice regarding smoking
	12240	137G.00	Trying to give up smoking
	30762	137d.00	Not interested in stopping smoking
	101338	137m.00	Failed attempt to stop smoking
	30423	137c.00	Thinking about stopping smoking
	2111	6791	Health ed. - smoking

	12941	1372.11	Occasional smoker
	10558	137R.00	Current smoker
	93	137P.00	Cigarette smoker
	12943	137J.00	Cigar smoker
	12947	137H.00	Pipe smoker
	34126	13p0.00	Negotiated date for cessation of smoking
	776	137K.00	Stopped smoking
	99838	137K000	Recently stopped smoking
	12878	137T.00	Date ceased smoking
	100495	137I.00	Ex roll-up cigarette smoker
	19488	137O.00	Ex cigar smoker
	90	137S.00	Ex smoker
	26470	137N.00	Ex pipe smoker
	97210	137j.00	Ex-cigarette smoker
	60	137L.00	Current non-smoker
	11788	1371.11	Non-smoker
BMI	8105	22K..00	Body Mass Index
	2	22A..00	O/E - weight
	3	229..00	O/E - height
	8105	22K..00	Body Mass Index
	9015	22K4.00	Body mass index index 25-29 - overweight
	126	22A6.00	O/E - Underweight
	2839	22A4.11	O/E - overweight

	22556	22K7.00	Body mass index 40+ - severely obese
	57111	22Z..00	Height and Weight

Table 2: Summary statistics for all clinical features included in the sensitivity analysis using corticosteroids to define GCA cases (n = 8244), matched to controls (n = 41,211), stratified by time prior to diagnosis.

	≤1 month prior				**6 months prior**				**12 months prior**				**24 months prior**			
	Cases		Controls		Cases		Controls		Cases		Controls		Cases		Controls	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Headache																
No	5695	69.08	41164	99.89	4927	59.76	41000	99.49	4721	57.27	40811	99.03	4531	54.96	40476	98.22
Yes	2549	30.92	47	0.11	3317	40.24	211	0.51	3523	42.73	400	0.97	3713	45.04	735	1.78
Fever																
No	8223	99.75	-	-	8214	99.64	41203	99.98	8203	99.50	41188	99.94	8193	99.38	41162	99.88
Yes	21	0.25	-	-	30	0.36	8	0.02	41	0.50	23	0.06	51	0.62	49	0.12
Elevated ESR																
No	6684	81.08	41152	99.86	5928	71.91	40925	99.31	5675	68.84	40816	99.04	5378	65.24	40771	98.93
Yes	1560	18.92	59	0.14	2316	28.09	286	0.69	2569	31.16	395	0.96	2866	34.76	440	1.07
Weight loss/																

Anorexia																
No	8191	99.36	41200	99.97	8121	98.51	41120	99.78	8080	98.01	41045	99.60	8005	97.10	40867	99.17
Yes	53	0.64	11	0.03	123	1.49	91	0.22	164	1.99	166	0.40	239	2.90	344	0.83
Visual impairment																
No	8219	99.70	41211	100.00	8198	99.44	-	-	8180	99.22	41204	99.98	8168	99.08	41195	99.96
Yes	25	0.30	0	0.00	46	0.56	-	-	64	0.78	7	0.02	76	0.92	16	0.04
Fatigue																
No	8223	99.75	-	-	8181	99.24	41171	99.90	8149	98.85	41131	99.81	8072	97.91	41025	99.55
Yes	21	0.25	-	-	63	0.76	40	0.10	95	1.15	80	0.19	172	2.09	186	0.45
Arthralgia/ Myalgia																
No	8228	99.81	-	-	8170	99.10	41179	99.92	8129	98.61	41142	99.83	8040	97.53	41087	99.70
Yes	16	0.19	-	-	74	0.90	32	0.08	115	1.39	69	0.17	204	2.47	124	0.30
Jaw pain																
No	8146	98.89	41211	100.00	82111	98.38	41211	100.00	8088	98.11	41198	99.97	8211	99.60	41182	99.30
	≤1 months prior				**6 months prior**				**12 months prior**				**24 months prior**			

	Cases		Controls		Cases		Controls		Cases		Controls		Cases		Controls	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Jaw pain - Yes	98	1.19	0	0.00	133	1.62	-	-	156	1.99	13	0.03	173	2.10	29	0.70
Comorbidities																
Hypertension (Read code)																
No	-	-	-	-	8079	98.00	40900	99.25	7970	96.68	40528	98.34	7682	93.18	39713	96.37
Yes	-	-	-	-	165	2.00	311	0.75	274	3.32	683	1.66	562	6.82	1498	3.63
Treated hypertension																
No	-	-	-	-	3719	45.11	30866	74.90	3567	43.27	30243	73.39	3367	40.84	29229	70.93
Yes	-	-	-	-	4525	54.89	10345	25.10	4677	56.73	10968	26.61	4877	59.16	11982	29.07
Cardiovascular/ Cerebrovascular diseases																
No	-	-	-	-	8082	98.03	40928	99.31	7930	96.19	40647	98.63	7675	93.10	40044	97.17

Yes	-	-	-	-	162	1.97	283	0.69	314	3.81	564	1.37	569	6.90	1167	2.83
Anxiety/ Depression																
No	-	-	-	-	8174	99.15	41090	99.71	8104	98.30	40976	99.43	7995	96.98	40742	98.86
Yes	-	-	-	-	70	0.85	121	0.29	140	1.70	235	0.57	249	3.02	469	1.14
PMR																
No	-	-	-	-	7510	91.10	41128	99.80	7364	89.33	41089	99.70	7189	87.20	41021	99.54
Yes	-	-	-	-	734	8.90	83	0.20	880	10.77	122	0.30	1055	12.80	190	0.46
Diabetes																
No	-	-	-	-	7927	96.15	40611	98.54	7706	93.47	39985	97.03	7499	90.96	39042	94.74
Yes	-	-	-	-	317	3.85	600	1.46	538	6.53	1226	2.97	745	9.04	1809	4.39
Cancer																
No	-	-	-	-	8211	99.60	41123	99.79	8186	99.30	41026	99.55	8141	98.75	40824	99.06
Yes	-	-	-	-	33		88	0.21	58	0.70	185	0.45	103	1.25	387	0.94

Table 3: Results from the conditional logistic regression fitted to the prescription sensitivity data, stratified by time prior to diagnosis of GCA, showing unadjusted and adjusted Odds ratios with 95% confidence intervals, for all clinical features.

	≤1 month prior				**6 months prior**				**12 months prior**				**24 months prior**			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Headache																
No	Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Yes	453.10	(312.20, 657.60)	430.54	(296.19, 625.83)	157.90	(129.80, 192.20)	146.10	(119.83, 178.13)	88.60	(76.62, 102.50)	80.52	(69.48, 93.32)	53.11	(47.43, 59.47)	47.34	(42.19, 53.12)
Fever																
No	-	-	-	-	Ref		Ref		Ref		Ref		Ref		Ref	
Yes	-	-	-	-	18.75	(8.60, 40.90)	17.50	(7.69, 39.87)	8.91	(5.35, 14.85)	7.38	(4.30, 12.67)	5.27	(3.55, 7.82)	4.19	(2.76, 6.35)
Weight loss/ Anorexia																

No	Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Yes	24.09	(12.58, 46.12)	19.41	(9.95, 37.84)	6.81	(5.19, 8.94)	5.54	(4.18, 7.35)	4.97	(4.01, 6.18)	3.99	(3.19, 4.99)	3.56	(3.01, 4.20)	2.80	(2.35, 3.33)
Elevated ESR																
No	Ref		Ref		Ref		Ref		Ref		Ref		Ref		Ref	
Yes	278.84	(196.45, 386.59)	265.65	(187.09, 372.61)	121.29	(102.75, 151.62)	112.93	(94.73, 139.03)	90.16	(43.67, 103.56)	83.68	(69.89, 98.32)	68.28	(59.16,78.82)	61.16	(52.86, 70.77)
Visual impairment																
No	-	-	-	-	-	-	-	-	Ref		Ref		Ref		Ref	
Yes	-	-	-	-	-	-	-	-	45.71	(20.95, 99.75)	41.91	(18.81, 93.38)	23.75	(13.85, 40.72)	19.86	(11.37, 34.69)
Fatigue																
No	-	-	-	-	Ref		Ref		Ref		Ref		Ref		Ref	
Yes	-	-	-	-	8.02	(5.38, 11.95)	6.38	(4.22, 9.64)	6.13	(4.53, 8.29)	5.04	(3.69, 6.89)	4.90	(3.96, 6.07)	3.88	(3.11, 4.84)

	≤1 month prior				6 months prior				12 months prior				24 months prior			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Arthralgia/ Myalgia																
No	-	-	-	-	Ref		Ref		Ref		Ref		Ref		Ref	
Yes	-	-	-	-	11.85	(7.79, 18.03)	9.85	(6.38, 15.19)	6.60	(6.35, 11.65)	6.90	(5.05, 9.43)	8.73	(6.94, 10.99)	6.88	(5.43, 8.72)
Jaw pain																
No	-	-	-	-	-	-	-	-	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	-	-	-	-	-	-	-	-	60.00	(34.07, 105.70)	52.02	(29.30, 92.36)	29.83	(20.13, 44.20)	24.19	(16.18, 36.17)
Comorbidities																
Hypertension (Read code)																

No	-	-	-	-	Ref		Ref		Ref		Ref		Ref		Ref	
Yes	-	-	-	-	2.70	(2.23, 3.27)	2.16	(1.77, 2.64)	2.09	(1.81, 2.42)	1.69	(1.45, 1.96)	2.01	(1.81, 2.23)	1.57	(1.41, 1.74)
Treated hypertension																
No	-	-	-	-	Ref		Ref		Ref		Ref		Ref		Ref	
Yes	-	-	-	-	3.90	(3.70, 4.10)	2.91	(2.75, 3.07)	3.90	(3.71, 4.11)	2.90	(2.74, 3.06)	3.83	(3.64, 4.03)	2.81	(2.66, 2.97)
Cardiovascular/ Cerebrovascular diseases																
No	-	-	-	-	Ref		Ref		Ref		Ref		Ref		Ref	
Yes	-	-	-	-	2.95	(2.42, 3.59)	2.33	(1.89, 2.86)	2.93	(2.54, 3.38)	2.36	(2.03, 2.74)	2.60	(2.34, 2.88)	2.08	(1.86, 2.32)
Anxiety/ Depression																

No	-	-	-	-	Ref		Ref		Ref		Ref		Ref		Ref	
Yes	-	-	-	-	2.95	(2.19, 3.98)	2.29	(1.68, 3.13)	3.09	(2.49, 3.83)	2.45	(1.95, 3.06)	2.78	(2.37, 3.25)	2.24	(1.90, 2.64)
	≤1 month prior				**6 months prior**				**12 months prior**				**24 months prior**			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
PMR																
No	-	-	-	-	Ref		Ref		Ref		Ref		Ref		Ref	
Yes	-	-	-	-	50.56	(39.69, 64.41)	47.10	(36.80, 60.30)	40.74	(33.33, 49.79)	37.20	(30.30, 45.68)	33.21	(28.07, 39.39)	30.24	(25.44, 35.95)
Diabetes																
No	-	-	-	-	Ref		Ref		Ref		Ref		Ref		Ref	

Yes	-	-	-	-	2.76	(2.40, 3.17)	2.33	(2.09, 2.59)	2.33	(2.09, 2.59)	1.65	(1.48, 1.84)	2.20	(2.012, 2.410)	1.57	(1.42, 1.72)
Cancer																
No	-	-	-	-	Ref		Ref		Ref		Ref		Ref		Ref	
Yes	-	-	-	-	1.88	(1.26, 2.80)	1.54	(1.02, 2.34)	1.57	(1.17, 2.12)	1.36	(1.01, 1.85)	1.34	(1.07, 1.66)	1.14	(1.05, 1.42)

Appendix 7.1 – Results from the LCA sensitivity analysis

Table 1: LCA results from the 4-class sensitivity model including constitutional symptoms. Showing the number in each class, the average posterior probability (AvePP) of each class, and class conditional outcome probability for each clinical feature.

Column1	**Class 1**	**Class 2**	**Class 3**	**Class 4**
	Class conditional outcome probabilities	Class conditional outcome probabilities	Class conditional outcome probabilities	Class conditional outcome probabilities
AvePP	0.83	0.71	0.78	0.8
Headache	45.40%	54.69%	29.90%	38.72%
Cancer	5.25%	3.86%	3.85%	3.51%
Visual	3.38%	2.77%	3.30%	3.22%
Treated hypertension	99.70%	40.46%	50.48%	34.65%
Cardiovascular diseases	30.57%	2.86%	4.19%	4.34%
Elevated ESR	30.89%	99.98%	46.55%	0.00%
Anxiety/ Depression	10.64%	5.45%	5.25%	7.05%
PMR	8.38%	4.12%	100.00%	2.12%

Arthralgia/ Myalgia	7.26%	5.75%	25.37%	4.72%
Diabetes	23.01%	5.52%	7.38%	3.33%
Jaw pain	1.74%	3.21%	2.15%	1.60%
Constitutional symptoms	13.85%	11.87%	13.84%	8.17%